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(71) Applicant (for all designated States except US):
JANSSEN PHARMACEUTICA N.V. [BE/BE]; Turnhoutseweg 30, B-2340 Beerse (BE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): VAN EMELEN,
Kristof [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). DE WINTER, Hans,
Louis, Jos [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). DYATKIN, Alexey,
Borisovich [RU/US]; Johnson & Johnson Pharmaceutical Research and Development, L.L.C., Welsh and McKean Roads, Springhouse, PA 19477 (US). VERDONCK, Marc, Gustaaf, Celine [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE). MEER-
POEL, Lieven [BE/BE]; Janssen Pharmaceutica N.V., Turnhoutseweg 30, B-2340 Beerse (BE).

(74) Common Representative: JANSSEN PHARMACEUTICA N.V.; Karen Vermuyten GA4736, J & J Patent Law Department, Turnhoutseweg 30, B-2340 Beerse (BE).

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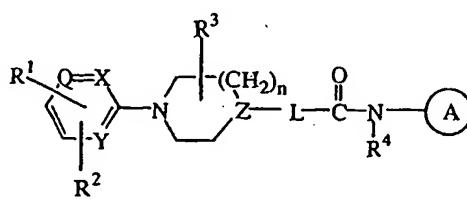
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(54) Title: AMINOCARBONYL-DERIVATIVES AS NOVEL INHIBITORS OF HISTONE DEACETYLASE



(I)

(57) Abstract: This invention comprises the novel compounds of formula (I) wherein n, R¹, R², R³, R⁴, L, Q, X, Y, Z and have defined meanings, having histone deacetylase inhibiting enzymatic activity; their preparation, compositions containing them and their use as a medicine.

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**AMINOCARBONYL-DERIVATIVES AS NOVEL INHIBITORS OF HISTONE
DEACETYLASE.**

This invention concerns compounds having histone deacetylase (HDAC) inhibiting

5 enzymatic activity. It further relates to processes for their preparation, to compositions comprising them, as well as their use, both *in vitro* and *in vivo*, to inhibit HDAC and as a medicine, for instance as a medicine to inhibit proliferative conditions, such as cancer and psoriasis.

10 In all eukaryotic cells, genomic DNA in chromatin associates with histones to form nucleosomes. Each nucleosome consists of a protein octamer made up of two copies of each histones H2A, H2B, H3 and H4. DNA winds around this protein core, with the basic amino acids of the histones interacting with the negatively charged phosphate groups of the DNA. The most common posttranslational modification of these core

15 histones is the reversible acetylation of the ε-amino groups of conserved, highly basic N-terminal lysine residues. The steady state of histone acetylation is established by the dynamic equilibrium between competing histone acetyltransferase(s) and histone deacetylase(s) herein referred to as "HDAC". Histone acetylation and deacetylation has long been linked to transcriptional control. The recent cloning of the genes encoding

20 different histone acetyltransferases and histone deacetylases provided a possible explanation for the relationship between histone acetylation and transcriptional control. The reversible acetylation of histones can result in chromatin remodelling and as such act as a control mechanism for gene transcription. In general, hyperacetylation of histones facilitates gene expression, whereas histone deacetylation is correlated with

25 transcriptional repression. Histone acetyltransferases were shown to act as transcriptional coactivators, whereas histone deacetylases were found to belong to transcriptional repression pathways.

The dynamic equilibrium between histone acetylation and deacetylation is essential for normal cell growth. Inhibition of histone deacetylase results in cell cycle arrest, cellular

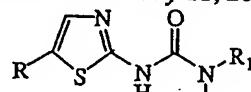
30 differentiation, apoptosis and reversal of the transformed phenotype. Therefore HDAC inhibitors can have great therapeutic potential in the treatment of cell proliferative diseases or conditions (Marks et al., Nature Reviews, Cancer 1: 194-202, 2001).

35 The study of inhibitors of histone deacetylases (HDAC) indicates that indeed these enzymes play an important role in cell proliferation and differentiation. The inhibitor Trichostatin A (TSA) causes cell cycle arrest at both G1 and G2 phases, reverts the transformed phenotype of different cell lines, and induces differentiation of Friend leukemia cells and others. TSA (and suberoylanilide hydroxamic acid SAHA) have

been reported to inhibit cell growth, induce terminal differentiation, and prevent the formation of tumours in mice (Finnin et al., Nature, 401: 188-193, 1999).

5 Trichostatin A has also been reported to be useful in the treatment of fibrosis, e.g. liver fibrosis and liver cirrhosis. (Geerts et al., European Patent Application EP 0 827 742, published 11 March, 1998).

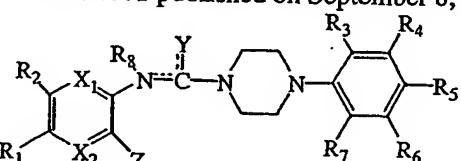
Patent application WO 00/26203 published on May 11, 2000 discloses cdk/cyclin



kinase inhibitors of general formula

10 pharmaceutical compositions containing these compounds, processes for their preparations and the use of these compounds for treating cell proliferative disorders associated with altered cell dependent kinase activity.

Patent application WO 00/52001 published on September 8, 2000 discloses compounds



15 of general formula , that demonstrate antitumor activities. It further provides processes for the preparations of these compounds.

20 Patent application WO01/38322 published on May 31, 2001 discloses amongst others inhibitors of histone deacetylase of general formula Cy-L¹-Ar-Y¹-C(O)-NH-Z, providing compositions and methods for treating cell proliferative diseases and conditions.

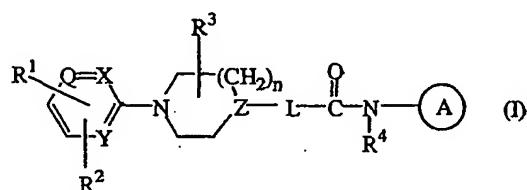
25 Patent application WO01/70675 published on 27 September, 2001 discloses inhibitors of histone deacetylase of formula Cy-X-Y¹-W or Cy-S(O)₂-NH-Y²-W and further provides compositions and methods for treating cell proliferative diseases and conditions.

30 The problem to be solved is to provide histone deacetylase inhibitors with high enzymatic activity and also show advantageous properties such as cellular activity and increased bioavailability; preferably oral bioavailability, and have little or no side effects.

The novel compounds of the present invention solve the above described problem. The compounds differ from the prior art in structure.

The compounds of the present invention show excellent *in-vitro* histone deacetylase inhibiting enzymatic activity. The present compounds have advantageous properties with regard to cellular activity and specific properties with regard to inhibition of cell cycle progression at both G1 and G2 checkpoints (p21 induction capacity). The compounds of the present invention show good metabolic stability and high bioavailability and more particular they show oral bioavailability.

This invention concerns compounds of formula (I)



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

n is 0, 1, 2 or 3 and when *n* is 0 then a direct bond is intended;

each Q is nitrogen or

each X is nitrogen or

each Y is nitrogen or

each Z is nitrogen or

R¹ is -C(O)NR⁷R⁸, -N(H)C(O)R⁹, -C(O)-C₁₋₆alkanediylSR⁹, -NR¹⁰C(O)N(OH)R⁹, -NR¹⁰C(O)C₁₋₆alkanediylSR⁹, -NR¹⁰C(O)C=N(OH)R⁹ or another Zn-chelating-

group
wherein R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl or aminoaryl;

R^9 is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, arylC₁₋₆alkyl, C₁₋₆alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl; R¹⁰ is independently selected from hydrogen or C₁₋₆alkyl;

5 R² is hydrogen, halo, hydroxy, amino, nitro, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl, di(C₁₋₆alkyl)amino, hydroxyamino or naphtalenylsulfonylpyrazinyl;

R³ is hydrogen, hydroxy, amino, hydroxyC₁₋₆alkyl, C₁₋₆alkyl, C₁₋₆alkyloxy, arylC₁₋₆alkyl, aminocarbonyl, hydroxycarbonyl, aminoC₁₋₆alkyl,

10 aminocarbonylC₁₋₆alkyl, hydroxycarbonylC₁₋₆alkyl, hydroxyaminocarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminoC₁₋₆alkyl or di(C₁₋₆alkyl)aminoC₁₋₆alkyl;

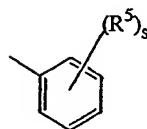
when Z is equal to nitrogen, then -L- is a direct bond;

when Z is equal to $\begin{array}{c} \text{CH} \\ \diagdown \\ \text{---} \end{array}$, then -L- is -NH- or the bivalent radical

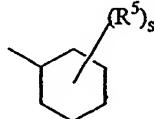
15 $\text{-C}_{1-6}\text{alkanediylNH-}$;

R⁴ is hydrogen, C₁₋₆alkyl, C₃₋₁₀cycloalkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, di(C₁₋₆alkyl)aminoC₁₋₆alkyl or aryl;

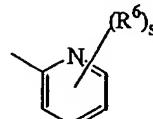
20 $\text{---}\circlearrowleft\text{A}$ is a radical selected from



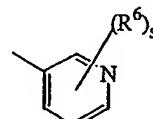
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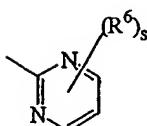
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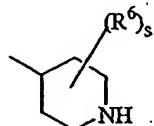
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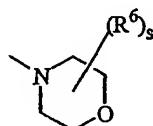
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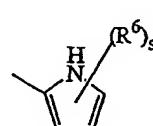
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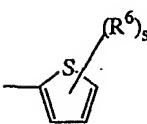
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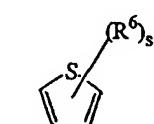
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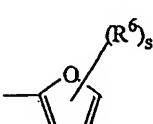
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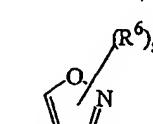
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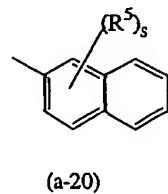
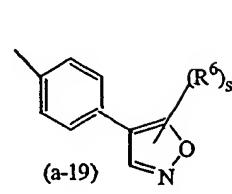
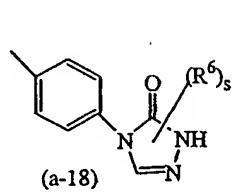
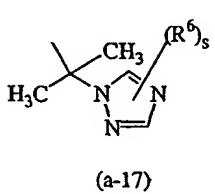
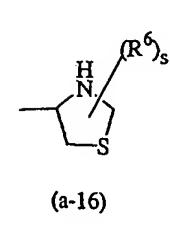
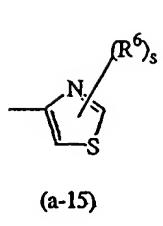
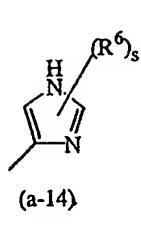
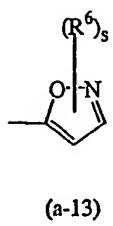
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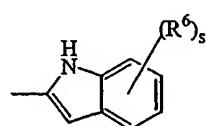
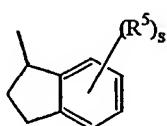
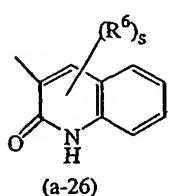
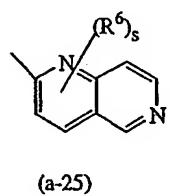
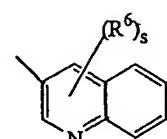
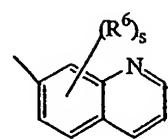
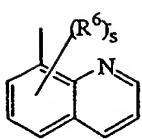
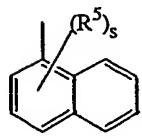
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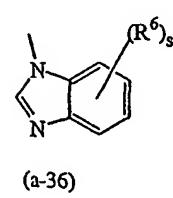
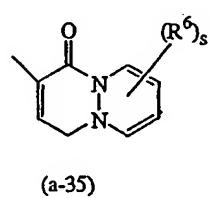
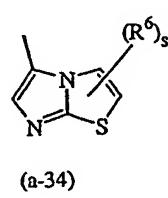
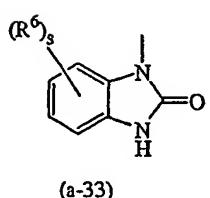
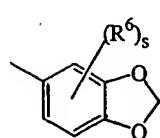
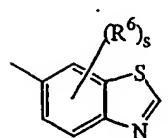
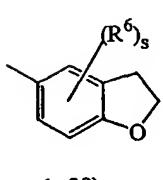
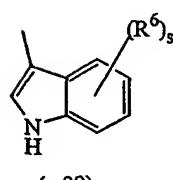
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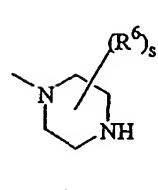
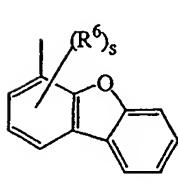
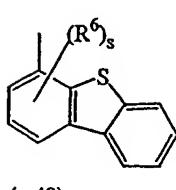
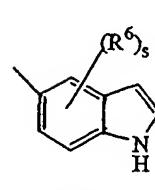
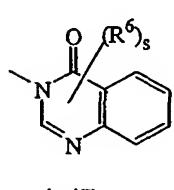
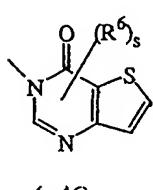
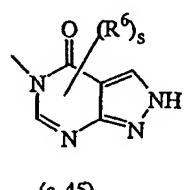
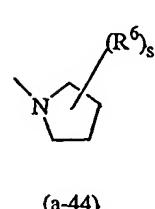
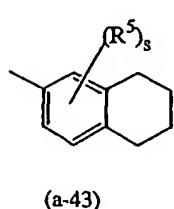
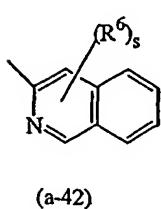
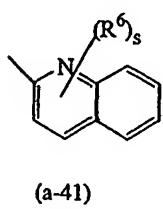
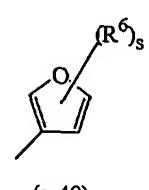
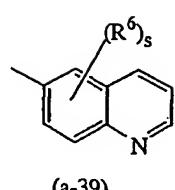
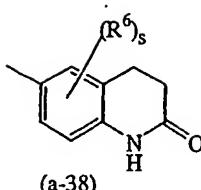
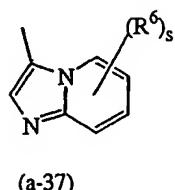
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-6-



wherein each s is independently 0, 1, 2, 3, 4 or 5;

each R⁵ and R⁶ are independently selected from hydrogen; halo; hydroxy; amino; nitro;

10 trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyl substituted with aryl and
C₃₋₁₀cycloalkyl; C₁₋₆alkyloxy; C₁₋₆alkyloxyC₁₋₆alkyloxy; C₁₋₆alkylcarbonyl;
C₁₋₆alkyloxycarbonyl; C₁₋₆alkylsulfonyl; cyanoC₁₋₆alkyl; hydroxyC₁₋₆alkyl;
hydroxyC₁₋₆alkyloxy; hydroxyC₁₋₆alkylamino; aminoC₁₋₆alkyloxy;

di(C₁₋₆alkyl)aminocarbonyl; di(hydroxyC₁₋₆alkyl)amino; (aryl)(C₁₋₆alkyl)amino;

15 di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy; di(C₁₋₆alkyl)aminoC₁₋₆alkylamino;

di(C₁₋₆alkyl)aminoC₁₋₆alkylaminoC₁₋₆alkyl; arylsulfonyl; arylsulfonylamino;

aryloxy; aryloxyC₁₋₆alkyl; arylC₂₋₆alkenediyl; di(C₁₋₆alkyl)amino;

di(C₁₋₆alkyl)aminoC₁₋₆alkyl; di(C₁₋₆alkyl)amino(C₁₋₆alkyl)amino;

di(C₁₋₆alkyl)amino(C₁₋₆alkyl)aminoC₁₋₆alkyl;

20 di(C₁₋₆alkyl)aminoC₁₋₆alkyl(C₁₋₆alkyl)amino;

di(C₁₋₆alkyl)aminoC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl;

aminosulfonylamino(C₁₋₆alkyl)amino;

aminosulfonylamino(C₁₋₆alkyl)aminoC₁₋₆alkyl;

di(C₁₋₆alkyl)aminosulfonylamino(C₁₋₆alkyl)amino;
di(C₁₋₆alkyl)aminosulfonylamino(C₁₋₆alkyl)aminoC₁₋₆alkyl; cyano; thiophenyl;
thiophenyl substituted with di(C₁₋₆alkyl)aminoC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl,
di(C₁₋₆alkyl)aminoC₁₋₆alkyl, C₁₋₆alkylpiperazinylC₁₋₆alkyl,

5 hydroxyC₁₋₆alkylpiperazinylC₁₋₆alkyl,
hydroxyC₁₋₆alkyloxyC₁₋₆alkylpiperazinylC₁₋₆alkyl,
di(C₁₋₆alkyl)aminosulfonylpiperazinylC₁₋₆alkyl,
C₁₋₆alkyloxypiperidinyl, C₁₋₆alkyloxypiperidinylC₁₋₆alkyl, morpholinylC₁₋₆alkyl,
hydroxyC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl, or di(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkyl;

10 furanyl; furanyl substituted with hydroxyC₁₋₆alkyl; benzofuranyl; imidazolyl;
oxazolyl; oxazolyl substituted with aryl and C₁₋₆alkyl; C₁₋₆alkyltriazolyl; tetrazolyl;
pyrrolidinyl; pyrrolyl; piperidinylC₁₋₆alkyloxy; morpholinyl; C₁₋₆alkylmorpholinyl;
morpholinylC₁₋₆alkyloxy;

15 morpholinylC₁₋₆alkyl; morpholinylC₁₋₆alkylamino;

20 morpholinylC₁₋₆alkylaminoC₁₋₆alkyl; piperazinyl; C₁₋₆alkylpiperazinyl;
C₁₋₆alkylpiperazinylC₁₋₆alkyloxy; piperazinylC₁₋₆alkyl;
naphtalenylsulfonylpiperazinyl; naphtalenylsulfonylpiperidinyl; naphtalenylsulfonyl:
C₁₋₆alkylpiperazinylC₁₋₆alkyl; C₁₋₆alkylpiperazinylC₁₋₆alkylamino;
C₁₋₆alkylpiperazinylC₁₋₆alkylaminoC₁₋₆alkyl; C₁₋₆alkylpiperazinylsulfonyl;

25 aminosulfonylpiperazinylC₁₋₆alkyloxy; aminosulfonylpiperazinyl;
aminosulfonylpiperazinylC₁₋₆alkyl; di(C₁₋₆alkyl)aminosulfonylpiperazinyl;
di(C₁₋₆alkyl)aminosulfonylpiperazinylC₁₋₆alkyl; hydroxyC₁₋₆alkylpiperazinyl;
hydroxyC₁₋₆alkylpiperazinylC₁₋₆alkyl; C₁₋₆alkyloxypiperidinyl;
C₁₋₆alkyloxypiperidinylC₁₋₆alkyl; piperidinylaminoC₁₋₆alkylamino;

30 25 piperidinylaminoC₁₋₆alkylaminoC₁₋₆alkyl;
(C₁₋₆alkylpiperidinyl)(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkylamino;
(C₁₋₆alkylpiperidinyl)(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkylaminoC₁₋₆alkyl;
hydroxyC₁₋₆alkyloxyC₁₋₆alkylpiperazinyl;
hydroxyC₁₋₆alkyloxyC₁₋₆alkylpiperazinylC₁₋₆alkyl;

35 30 (hydroxyC₁₋₆alkyl)(C₁₋₆alkyl)amino; (hydroxyC₁₋₆alkyl)(C₁₋₆alkyl)aminoC₁₋₆alkyl;
hydroxyC₁₋₆alkylaminoC₁₋₆alkyl; di(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkyl;
pyrrolidinylC₁₋₆alkyl; pyrrolidinylC₁₋₆alkyloxy; pyrazolyl; thiopyrazolyl; pyrazolyl
substituted with two substituents selected from C₁₋₆alkyl or trihaloC₁₋₆alkyl;
pyridinyl; pyridinyl substituted with C₁₋₆alkyloxy, aryloxy or aryl; pyrimidinyl;
tetrahydropyrimidinylpiperazinyl; tetrahydropyrimidinylpiperazinylC₁₋₆alkyl;
quinolinyl; indolyl; phenyl; phenyl substituted with one, two or three substituents
independently selected from halo, amino, nitro, C₁₋₆alkyl, C₁₋₆alkyloxy,
hydroxyC₁₋₄alkyl, trifluoromethyl, trifluoromethoxy, hydroxyC₁₋₄alkyloxy,

C₁₋₄alkylsulfonyl, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkyloxycarbonyl,
aminoC₁₋₄alkyloxy, di(C₁₋₄alkyl)aminoC₁₋₄alkyloxy, di(C₁₋₄alkyl)amino,
di(C₁₋₄alkyl)aminocarbonyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl,
di(C₁₋₄alkyl)aminoC₁₋₄alkylaminoC₁₋₄alkyl,

5 di(C₁₋₄alkyl)amino(C₁₋₄alkyl)amino, di(C₁₋₄alkyl)amino(C₁₋₄alkyl)aminoC₁₋₄alkyl,
di(C₁₋₄alkyl)aminoC₁₋₄alkyl(C₁₋₄alkyl)amino,
di(C₁₋₄alkyl)aminoC₁₋₄alkyl(C₁₋₄alkyl)aminoC₁₋₄alkyl,
aminosulfonylamino(C₁₋₄alkyl)amino,
aminosulfonylamino(C₁₋₄alkyl)aminoC₁₋₄alkyl,

10 di(C₁₋₄alkyl)aminosulfonylamino(C₁₋₄alkyl)amino,
di(C₁₋₄alkyl)aminosulfonylamino(C₁₋₄alkyl)aminoC₁₋₆alkyl, cyano,
piperidinylC₁₋₄alkyloxy, pyrrolidinylC₁₋₄alkyloxy, aminosulfonylpiperazinyl,
aminosulfonylpiperazinylC₁₋₄alkyl, di(C₁₋₄alkyl)aminosulfonylpiperazinyl,
di(C₁₋₄alkyl)aminosulfonylpiperazinylC₁₋₄alkyl, hydroxyC₁₋₄alkylpiperazinyl,

15 hydroxyC₁₋₄alkylpiperazinylC₁₋₄alkyl, C₁₋₄alkyloxypiperidinyl,
C₁₋₄alkyloxypiperidinylC₁₋₄alkyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkylpiperazinyl,
hydroxyC₁₋₄alkyloxyC₁₋₄alkylpiperazinylC₁₋₄alkyl,
(hydroxyC₁₋₄alkyl)(C₁₋₄alkyl)amino, (hydroxyC₁₋₄alkyl)(C₁₋₄alkyl)aminoC₁₋₄alkyl,
di(hydroxyC₁₋₄alkyl)amino, di(hydroxyC₁₋₄alkyl)aminoC₁₋₄alkyl, furanyl, furanyl

20 substituted with -CH=CH-CH=CH-, pyrrolidinylC₁₋₄alkyl, pyrrolidinylC₁₋₄alkyloxy,
morpholinyl, morpholinylC₁₋₄alkyloxy, morpholinylC₁₋₄alkyl,
morpholinylC₁₋₄alkylamino, morpholinylC₁₋₄alkylaminoC₁₋₄alkyl, piperazinyl,
C₁₋₄alkylpiperazinyl, C₁₋₄alkylpiperazinylC₁₋₄alkyloxy, piperazinylC₁₋₄alkyl,
C₁₋₄alkylpiperazinylC₁₋₄alkyl, C₁₋₄alkylpiperazinylC₁₋₄alkylamino,

25 C₁₋₄alkylpiperazinylC₁₋₄alkylaminoC₁₋₆alkyl, tetrahydropyrimidinylpiperazinyl,
tetrahydropyrimidinylpiperazinylC₁₋₄alkyl, piperidinylaminoC₁₋₄alkylamino,
piperidinylaminoC₁₋₄alkylaminoC₁₋₄alkyl,
(C₁₋₄alkylpiperidinyl)(hydroxyC₁₋₄alkyl)aminoC₁₋₄alkylamino,
(C₁₋₄alkylpiperidinyl)(hydroxyC₁₋₄alkyl)aminoC₁₋₄alkylaminoC₁₋₄alkyl,

30 pyridinylC₁₋₄alkyloxy,
hydroxyC₁₋₄alkylamino, hydroxyC₁₋₄alkylaminoC₁₋₄alkyl,
di(C₁₋₄alkyl)aminoC₁₋₄alkylamino, aminothiadiazolyl,
aminosulfonylpiperazinylC₁₋₄alkyloxy, or thiophenylC₁₋₄alkylamino;
each R⁵ and R⁶ can be placed on the nitrogen in replacement of the hydrogen;

35 aryl in the above is phenyl, or phenyl substituted with one or more substituents each
independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl, cyano or
hydroxycarbonyl.

The term "histone deacetylase inhibitor" or "inhibitor of histone deacetylase" is used to identify a compound, which is capable of interacting with a histone deacetylase and inhibiting its activity, more particularly its enzymatic activity. Inhibiting histone deacetylase enzymatic activity means reducing the ability of a histone deacetylase to remove an acetyl group from a histone. Preferably, such inhibition is specific, i.e. the histone deacetylase inhibitor reduces the ability of a histone deacetylase to remove an acetyl group from a histone at a concentration that is lower than the concentration of the inhibitor that is required to produce some other, unrelated biological effect.

As used in the foregoing definitions and hereinafter, halo is generic to fluoro, chloro, bromo and iodo; C₁₋₄alkyl defines straight and branched chain saturated hydrocarbon radicals having from 1 to 4 carbon atoms such as, e.g. methyl, ethyl, propyl, butyl, 1-methylethyl, 2-methylpropyl and the like; C₁₋₆alkyl includes C₁₋₄alkyl and the higher homologues thereof having 5 to 6 carbon atoms such as, for example, pentyl, 2-methylbutyl, hexyl, 2-methylpentyl and the like; C₁₋₆alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof such as, 2-methylpentanediyl, 3-methylpentanediyl, 2,2-dimethylbutanediyl, 2,3-dimethylbutanediyl and the like; trihaloC₁₋₆alkyl defines C₁₋₆alkyl containing three identical or different halo substituents for example trifluoromethyl; C₂₋₆alkenediyl defines bivalent straight and branched chain hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example, ethenediyl, 2-propenediyl, 3-butenediyl, 2-pentenediyl, 3-pentenediyl, 3-methyl-2-butenediyl, and the like; aryl defines phenyl, and phenyl substituted with one or more substituents each independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl, cyano, hydroxycarbonyl; aminoaryl defines aryl substituted with amino; C₃₋₁₀cycloalkyl includes cyclic hydrocarbon groups having from 3 to 10 carbons, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl and the like.

The term "another Zn-chelating group" refers to a group which is capable of interacting with a Zn-ion, which can be present at an enzymatic binding site.

Pharmaceutically acceptable addition salts encompass pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts. The pharmaceutically acceptable acid addition salts as mentioned hereinabove are meant to

comprise the therapeutically active non-toxic acid addition salt forms which the compounds of formula (I) are able to form. The compounds of formula (I) which have basic properties can be converted in their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise,

5 for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, trifluoroacetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (*i.e.* butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, cyclamic,

10 salicylic, *p*-amino-salicylic, pamoic and the like acids.

The compounds of formula (I) which have acidic properties may be converted in their pharmaceutically acceptable base addition salts by treating said acid form with a suitable organic or inorganic base. Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, *N*-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

15 The term "acid or base addition salts" also comprises the hydrates and the solvent addition forms which the compounds of formula (I) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

20 The term "stereochemically isomeric forms of compounds of formula (I)", as used herein, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formula (I) may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the

25 compounds of formula (I) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

30 The *N*-oxide forms of the compounds of formula (I) are meant to comprise those compounds of formula (I) wherein one or several nitrogen atoms are oxidized to the so-called *N*-oxide, particularly those *N*-oxides wherein one or more of the piperidine-, piperazine or pyridazinyl-nitrogens are *N*-oxidized.

35 Some of the compounds of formula (I) may also exist in their tautomeric forms. Such

forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formula (I)" is meant to include
5 also the pharmaceutically acceptable addition salts and all stereoisomeric forms.

As used herein, the terms "histone deacetylase" and "HDAC" are intended to refer to any one of a family of enzymes that remove acetyl groups from the ε-amino groups of lysine residues at the N-terminus of a histone. Unless otherwise indicated by context,
10 the term "histone" is meant to refer to any histone protein, including H1, H2A, H2B, H3, H4, and H5, from any species. Human HDAC proteins or gene products, include, but are not limited to, HDAC-1, HDAC-2, HDAC-3, HDAC-4, HDAC-5, HDAC-6, HDAC-7, HDAC-8, HDAC-9 and HDAC-10. The histone deacetylase can also be derived from a protozoal or fungal source.

15

A first group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply:

- a) n is 1;
- b) each Q is $\text{---C}\equiv\text{---}$;
- c) R^1 is $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or $-\text{NHC}(\text{O})\text{C}_{1-6}\text{alkanediylSH}$ wherein R^7 and R^8 are each independently selected from hydrogen, hydroxy or hydroxy C_{1-6} alkyl;
- d) R^2 is hydrogen or nitro;
- e) R^3 is hydrogen;
- f) when Z is equal to $\text{---CH}\leftarrow$, then $-L-$ is the bivalent radical $-\text{C}_{1-6}\text{alkanediylNH}-$;
- 25 g) R^4 is hydrogen, C_{1-6} alkyl or aryl;
- h) $\text{---}\bigcirc\text{A}\text{---}$ is a radical selected from (a-1) or (a-21);
- i) each s is independently 0, 1 or 2;
- j) each R^5 is independently selected from hydrogen; halo; trihalo C_{1-6} alkyl;
30 trihalo C_{1-6} alkyloxy; C_{1-6} alkyl; C_{1-6} alkyloxy; C_{1-6} alkylcarbonyl; aryloxy; cyano or phenyl.

A second group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply:

- a) n is 1;
- 35 b) each Q is $\text{---C}\equiv\text{---}$;
- c) each X is nitrogen;
- d) each Y is nitrogen;

e) R¹ is -C(O)NH(OH);
f) R² is hydrogen;
g) R³ is hydrogen;
h) when Z is equal to ---CH--- , then -L- is the bivalent radical -C₁₋₆alkanediylNH-;
5 i) R⁴ is hydrogen, C₁₋₆alkyl or aryl;
j) ---A--- is the radical (a-1);
k) each s is independently 0 or 1;
l) each R⁵ is independently selected from hydrogen or phenyl.

10 A third group of interesting compounds consists of those compounds of formula (I) wherein one or more of the following restrictions apply:
a) each Z is nitrogen;
b) R¹ is -C(O)NR⁷R⁸, -C(O)-C₁₋₆alkanediylSR⁹, -NR¹⁰C(O)N(OH)R⁹,
-NR¹⁰C(O)C₁₋₆alkanediylSR⁹, -NR¹⁰C(O)C=N(OH)R⁹ or another

15 Zn-chelating-group
wherein R⁷ and R⁸ are each independently selected from hydrogen, hydroxy,
hydroxyC₁₋₆alkyl, or aminoC₁₋₆alkyl;
c) R² is hydrogen, halo, hydroxy, amino, nitro, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl
or di(C₁₋₆alkyl)amino;

20 d) R³ is hydrogen, hydroxy, amino, hydroxyC₁₋₆alkyl, C₁₋₆alkyl, C₁₋₆alkyloxy,
arylC₁₋₆alkyl, aminocarbonyl, aminoC₁₋₆alkyl, C₁₋₆alkylaminoC₁₋₆alkyl or
di(C₁₋₆alkyl)aminoC₁₋₆alkyl;
e) R⁴ is hydrogen;
f) ---A--- is a radical selected from (a-1), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-9),
(a-10), (a-11), (a-12), (a-13), (a-14), (a-15), (a-16), (a-17), (a-18), (a-19), (a-20),
(a-21), (a-22), (a-23), (a-24), (a-25), (a-26), (a-28), (a-29), (a-30), (a-31), (a-32),
(a-33), (a-34), (a-35), (a-36), (a-37), (a-38), (a-39), (a-40), (a-41), (a-42), (a-44),
(a-45), (a-46), (a-47), (a-48) or (a-51);
g) each s is independently 0, 1, 2, 3 or 4;

30 h) R⁵ is hydrogen; halo; hydroxy; amino; nitro; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy;
C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl;
C₁₋₆alkylsulfonyl; hydroxyC₁₋₆alkyl; aryloxy; di(C₁₋₆alkyl)amino; cyano;
thiophenyl; furanyl; furanyl substituted with hydroxyC₁₋₆alkyl; benzofuranyl;
imidazolyl; oxazolyl; oxazolyl substituted with aryl and C₁₋₆alkyl;
35 C₁₋₆alkyltriazolyl; tetrazolyl; pyrrolidinyl; pyrrolyl; morpholinyl;
C₁₋₆alkylmorpholinyl; piperazinyl; C₁₋₆alkylpiperazinyl;

hydroxyC₁₋₆alkylpiperazinyl; C₁₋₆alkyloxypiperidinyl; pyrazolyl; pyrazolyl substituted with one or two substituents selected from C₁₋₆alkyl or trihaloC₁₋₆alkyl; pyridinyl; pyridinyl substituted with C₁₋₆alkyloxy, aryloxy or aryl; pyrimidinyl; quinolinyl; indole; phenyl; or phenyl substituted with one or two substituents independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl;

5 i) R⁶ is hydrogen; halo; hydroxy; amino; nitro; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylsulfonyl; hydroxyC₁₋₆alkyl; aryloxy; di(C₁₋₆alkyl)amino; cyano; pyridinyl; phenyl; or phenyl substituted with one or two substituents independently selected

10 from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl.

A group of preferred compounds consists of those compounds of formula (I) wherein each Z is nitrogen;

R¹ is -C(O)NR⁷R⁸, -C(O)-C₁₋₆alkanediylSR⁹, -NR¹⁰C(O)N(OH)R⁹,

15 -NR¹⁰C(O)C₁₋₆alkanediylSR⁹, -NR¹⁰C(O)C=N(OH)R⁹ or another Zn-chelating-group
wherein R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, hydroxyC₁₋₆alkyl, or aminoC₁₋₆alkyl;

R² is hydrogen, halo, hydroxy, amino, nitro, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl or
20 di(C₁₋₆alkyl)amino;

R³ is hydrogen, hydroxy, amino, hydroxyC₁₋₆alkyl, C₁₋₆alkyl, C₁₋₆alkyloxy, arylC₁₋₆alkyl, aminocarbonyl, aminoC₁₋₆alkyl, C₁₋₆alkylaminoC₁₋₆alkyl or di(C₁₋₆alkyl)aminoC₁₋₆alkyl;

R⁴ is hydrogen;

25 —(A) is a radical selected from (a-1), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-9), (a-10), (a-11), (a-12), (a-13), (a-14), (a-15), (a-16), (a-17), (a-18), (a-19), (a-20), (a-21), (a-22), (a-23), (a-24), (a-25), (a-26), (a-28), (a-29), (a-30), (a-31), (a-32), (a-33), (a-34), (a-35), (a-36), (a-37), (a-38), (a-39), (a-40), (a-41), (a-42), (a-44), (a-45), (a-46), (a-47), (a-48) or (a-51);

30 each s is independently 0, 1, 2, 3 or 4;

R⁵ is hydrogen; halo; hydroxy; amino; nitro; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylsulfonyl; hydroxyC₁₋₆alkyl; aryloxy; di(C₁₋₆alkyl)amino; cyano; thiophenyl; furanyl; furanyl substituted with hydroxyC₁₋₆alkyl; benzofuranyl;

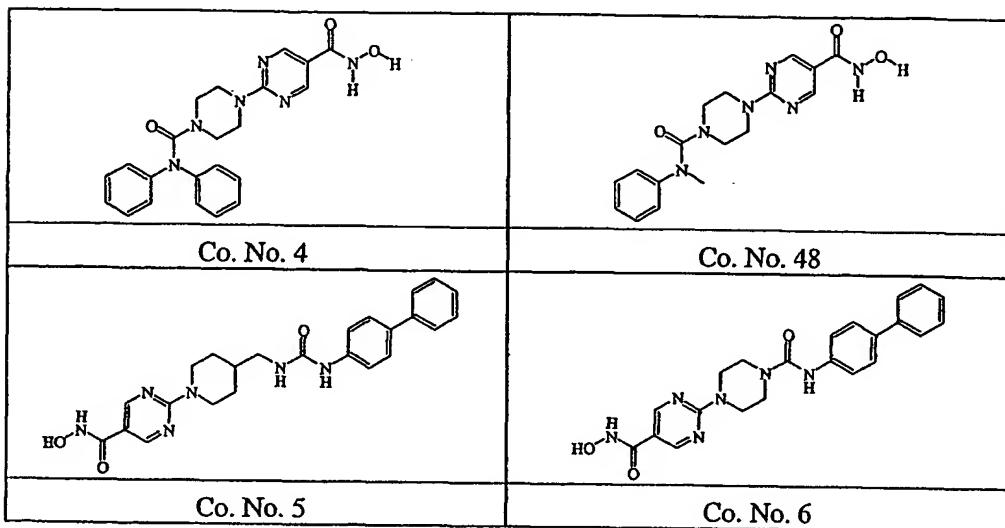
35 imidazolyl; oxazolyl; oxazolyl substituted with aryl and C₁₋₆alkyl; C₁₋₆alkyltriazolyl; tetrazolyl; pyrrolidinyl; pyrrolyl; morpholinyl; C₁₋₆alkylmorpholinyl; piperazinyl; C₁₋₆alkylpiperazinyl;

hydroxyC₁₋₆alkylpiperazinyl; C₁₋₆alkyloxypiperidinyl; pyrazolyl; pyrazolyl substituted with one or two substituents selected from C₁₋₆alkyl or trihaloC₁₋₆alkyl; pyridinyl; pyridinyl substituted with C₁₋₆alkyloxy, aryloxy or aryl; pyrimidinyl; quinolinyl; indole; phenyl; or phenyl substituted with one or two substituents independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl; and R⁶ is hydrogen; halo; hydroxy; amino; nitro; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylsulfonyl; hydroxyC₁₋₆alkyl; aryloxy; di(C₁₋₆alkyl)amino; cyano; pyridinyl; phenyl; or phenyl substituted with one or two substituents independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl.

Another group of preferred compounds consists of those compounds of formula (I) wherein n is 1; each Q is $\text{---}\text{C}\equiv\text{}$; R¹ is $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, or -NHC(O)C₁₋₆alkanediylSH wherein R⁷ and R⁸ are each independently selected from hydrogen, hydroxy or hydroxyC₁₋₆alkyl; R² is hydrogen or nitro; R³ is hydrogen; when Z is equal to $-\text{CH}\equiv\text{}$, then -L- is the bivalent radical $-\text{C}_1\text{-6alkanediylNH-}$; R⁴ is hydrogen, C₁₋₆alkyl or aryl; $-\text{A}^\circ$ is a radical selected from (a-1) or (a-21); each s is independently 0, 1 or 2; and each R⁵ is independently selected from hydrogen; halo; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; aryloxy; cyano or phenyl.

A group of more preferred compounds consists of those compounds of formula (I) wherein n is 1; each Q is $\text{---}\text{C}\equiv\text{}$; each X is nitrogen; each Y is nitrogen; R¹ is $-\text{C}(\text{O})\text{NH}(\text{OH})$; R² is hydrogen; R³ is hydrogen; when Z is equal to $-\text{CH}\equiv\text{}$, then -L- is the bivalent radical $-\text{C}_1\text{-6alkanediylNH-}$; R⁴ is hydrogen, C₁₋₆alkyl or aryl; $-\text{A}^\circ$ is the radical (a-1); each s is independently 0 or 1; and each R⁵ is independently selected from hydrogen or phenyl.

Most preferred compounds are compounds No. 4, No. 48, No. 5 and No. 6.

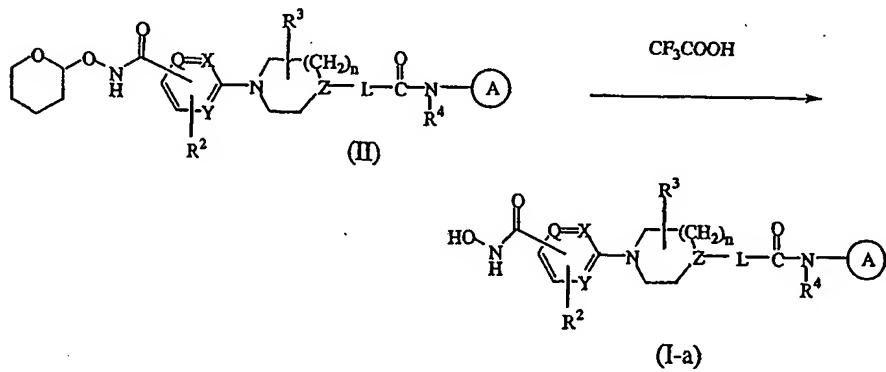


The compounds of formula (I) and their pharmaceutically acceptable salts and N-oxides

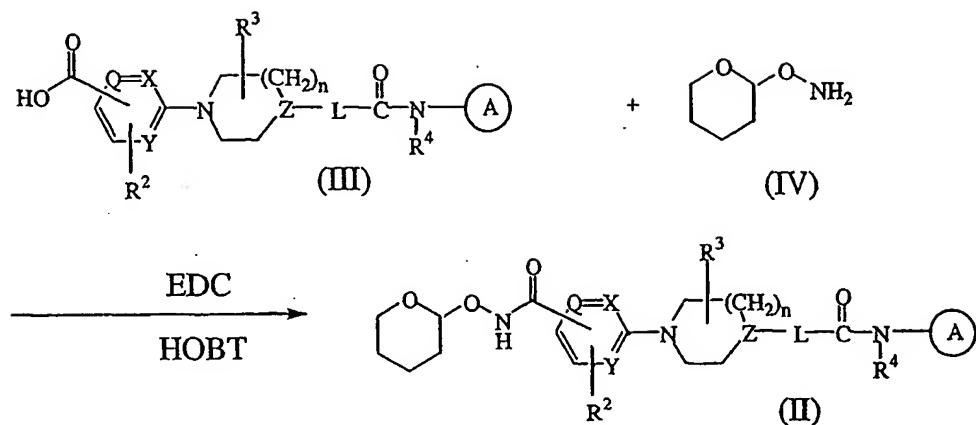
5 and stereochemically isomeric forms thereof may be prepared in conventional manner.

A general synthesis routes is encompassed as example:

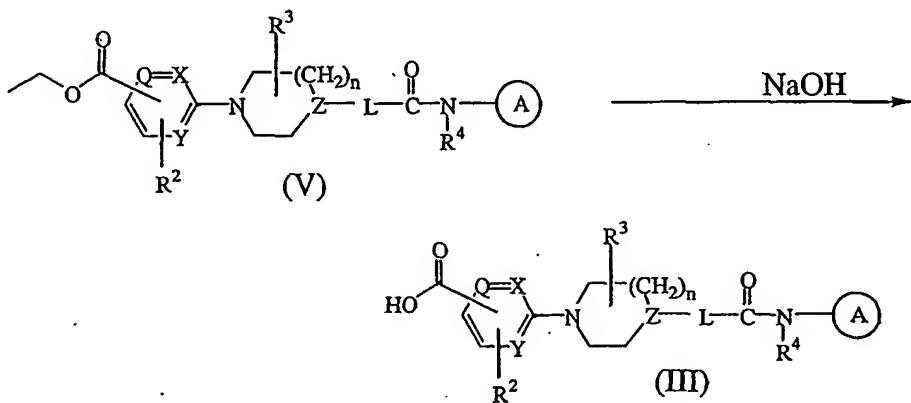
a) Hydroxamic acids of formula (I) wherein R¹ is -C(O)NH(OH), said compounds
being referred to as compounds of formula (I-a), may be prepared by reacting an
intermediate of formula (II) with an appropriate acid, such as for example, trifluoro
10 acetic acid. Said reaction is performed in an appropriate solvent, such as, for example,
methanol.



b) intermediates of formula (II) may be prepared by reacting an intermediate of formula
15 (III) with an intermediate of formula (IV) in the presence of appropriate reagents such
as N-(ethylcarbonimidoyl)-N,N-dimethyl-1,3-propanediamine, monohydrochloride
(EDC) and 1-hydroxy-1*H*-benzotriazole (HOBT). The reaction may be performed in a
suitable solvent such as a mixture of dichloromethane and tetrahydrofuran.



c) intermediates of formula (III) may be prepared by reacting an intermediate of
 5 formula (V) with an appropriate base such as NaOH in the presence of a suitable solvent such as ethanol.



10 The compounds of formula (I) can also conveniently be prepared using solid phase synthesis techniques. In general, solid phase synthesis involves reacting an intermediate in a synthesis with a polymer support. This polymer-supported intermediate can then be carried on through a number of synthesis steps. After each step, filtering the resin and washing it numerous times with various solvents remove impurities. At each
 15 step the resin can be split up to react with various intermediates in the next step thus allowing for the synthesis of a large number of compounds. After the last step in the procedure the resin is treated with a reagent or process to cleave the resin from the sample. More detailed explanation of the techniques used in solid phase chemistry is described in for example "The Combinatorial Index" (B.Bunin, Academic Press) and

Novabiochem's 1999 Catalogue & Peptide Synthesis Handbook (Novabiochem AG, Switzerland) both incorporated herein by reference.

The compounds of formula (I) and some of the intermediates may have at least one stereogenic centre in their structure. This stereogenic centre may be present in an R or an S configuration.

The compounds of formula (I) as prepared in the hereinabove described processes are generally racemic mixtures of enantiomers, which can be separated from one another following art-known resolution procedures. The racemic compounds of formula (I) may be converted into the corresponding diastereomeric salt forms by reaction with a suitable chiral acid. Said diastereomeric salt forms are subsequently separated, for example, by selective or fractional crystallization and the enantiomers are liberated there from by alkali. An alternative manner of separating the enantiomeric forms of the compounds of formula (I) involves liquid chromatography using a chiral stationary phase. Said pure stereochemically isomeric forms may also be derived from the corresponding pure stereochemically isomeric forms of the appropriate starting materials, provided that the reaction occurs stereospecifically. Preferably if a specific stereoisomer is desired, said compound would be synthesized by stereospecific methods of preparation. These methods will advantageously employ enantiomerically pure starting materials.

The compounds of formula (I), the pharmaceutically acceptable acid addition salts and stereoisomeric forms thereof have valuable pharmacological properties in that they have a histone deacetylase (HDAC) inhibitory effect.

This invention provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a compound of the invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g. loss of contact inhibition). This includes the inhibition of tumour growth both directly by causing growth arrest, terminal differentiation and/or apoptosis of cancer cells, and indirectly, by inhibiting neovascularization of tumours.

This invention also provides a method for inhibiting tumour growth by administering an effective amount of a compound of the present invention, to a subject, e.g. a mammal (and more particularly a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumours by the administration of an effective amount of the compounds of the present invention. Examples of

tumours which may be inhibited, but are not limited to, lung cancer (e.g. adenocarcinoma and including non-small cell lung cancer), pancreatic cancers (e.g. pancreatic carcinoma such as, for example exocrine pancreatic carcinoma), colon cancers (e.g. colorectal carcinomas, such as, for example, colon adenocarcinoma and 5 colon adenoma), prostate cancer including the advanced disease, hematopoietic tumours of lymphoid lineage (e.g. acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), tumours of mesenchymal origin (e.g. fibrosarcomas and rhabdomyosarcomas), melanomas, 10 teratocarcinomas, neuroblastomas, gliomas, benign tumour of the skin (e.g. keratoacanthomas), breast carcinoma (e.g. advanced breast cancer), kidney carcinoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma.

The compound according to the invention may be used for other therapeutic purposes, 15 for example:

- a) the sensitisation of tumours to radiotherapy by administering the compound according to the invention before, during or after irradiation of the tumour for treating cancer;
- b) treating arthropathies and osteopathological conditions such as rheumatoid 20 arthritis, osteoarthritis, juvenile arthritis, gout, polyarthritis, psoriatic arthritis, ankylosing spondylitis and systemic lupus erythematosus;
- c) inhibiting smooth muscle cell proliferation including vascular proliferative disorders, atherosclerosis and restenosis;
- d) treating inflammatory conditions and dermal conditions such as ulcerative 25 colitis, Crohn's disease, allergic rhinitis, graft vs. host disease, conjunctivitis, asthma, ARDS, Behcets disease, transplant rejection, urticaria, allergic dermatitis, alopecia areata, scleroderma, exanthema, eczema, dermatomyositis, acne, diabetes, systemic lupus erythematosis, Kawasaki's disease, multiple sclerosis, emphysema, cystic fibrosis and chronic bronchitis;
- e) treating endometriosis, uterine fibroids, dysfunctional uterine bleeding and 30 endometrial hyperplasia;
- f) treating ocular vascularisation including vasculopathy affecting retinal and choroidal vessels;
- g) treating a cardiac dysfunction;
- h) inhibiting immunosuppressive conditions such as the treatment of HIV 35 infections;
- i) treating renal dysfunction;
- j) suppressing endocrine disorders;

- k) inhibiting dysfunction of gluconeogenesis;
- l) treating a neuropathology for example Parkinson's disease or a neuropathology that results in a cognitive disorder, for example, Alzheimer's disease or polyglutamine related neuronal diseases;
- 5 m) inhibiting a neuromuscular pathology, for example, amyotrophic lateral sclerosis;
- n) treating spinal muscular atrophy;
- o) treating other pathologic conditions amenable to treatment by potentiating expression of a gene;
- 10 p) enhancing gene therapy.

Hence, the present invention discloses the compounds of formula (I) for use as a medicine as well as the use of these compounds of formula (I) for the manufacture of a medicament for treating one or more of the above mentioned conditions.

15

The compounds of formula (I), the pharmaceutically acceptable acid addition salts and stereoisomeric forms thereof can have valuable diagnostic properties in that they can be used for detecting or identifying a HDAC in a biological sample comprising detecting or measuring the formation of a complex between a labelled compound and a HDAC.

20

The detecting or identifying methods can use compounds that are labelled with labelling agents such as radioisotopes, enzymes, fluorescent substances, luminous substances, etc. Examples of the radioisotopes include ^{125}I , ^{131}I , ^3H and ^{14}C . Enzymes are usually made detectable by conjugation of an appropriate substrate which, in turn catalyses a detectable reaction. Examples thereof include, for example, beta-galactosidase, beta-glucosidase, alkaline phosphatase, peroxidase and malate dehydrogenase, preferably horseradish peroxidase. The luminous substances include, for example, luminol, luminol derivatives, luciferin, aequorin and luciferase.

30

Biological samples can be defined as body tissue or body fluids. Examples of body fluids are cerebrospinal fluid, blood, plasma, serum, urine, sputum, saliva and the like.

In view of their useful pharmacological properties, the subject compounds may be formulated into various pharmaceutical forms for administration purposes.

35

To prepare the pharmaceutical compositions of this invention, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which

carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form,
5 any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets.

10 Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for
15 example, may be included. Injectable solutions, for example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier optionally comprises
20 a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a
25 transdermal patch, as a spot-on or as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically
30 discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient, calculated to produce the desired therapeutic effect, in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and
35 segregated multiples thereof.

Those skilled in the art could easily determine the effective amount from the test results presented hereinafter. In general it is contemplated that a therapeutically effective

amount would be from 0.05 mg/kg to 100 mg/kg body weight, and in particular from 0.05 mg/kg to 10 mg/kg body weight. It may be appropriate to administer the required dose as two, three, four or more sub-doses at appropriate intervals throughout the day. Said sub-doses may be formulated as unit dosage forms, for example, containing 0.5 to 5 500 mg, and in particular 10 mg to 500 mg of active ingredient per unit dosage form.

As another aspect of the present invention a combination of a HDAC-inhibitor with another anticancer agent is envisaged, especially for use as a medicine, more specifically in the treatment of cancer or related diseases.

10

For the treatment of the above conditions, the compounds of the invention may be advantageously employed in combination with one or more other medicinal agents, more particularly, with other anti-cancer agents. Examples of anti-cancer agents are:

15

- platinum coordination compounds for example cisplatin, carboplatin or oxaliplatin;
- taxane compounds for example paclitaxel or docetaxel;
- topoisomerase I inhibitors such as camptothecin compounds for example irinotecan or topotecan;
- topoisomerase II inhibitors such as anti-tumour podophyllotoxin derivatives for example etoposide or teniposide;
- anti-tumour vinca alkaloids for example vinblastine, vincristine or vinorelbine;
- anti-tumour nucleoside derivatives for example 5-fluorouracil, gemcitabine or capecitabine;
- alkylating agents such as nitrogen mustard or nitrosourea for example cyclophosphamide, chlorambucil, carmustine or lomustine;
- anti-tumour anthracycline derivatives for example daunorubicin, doxorubicin, idarubicin or mitoxantrone;
- HER2 antibodies for example trastuzumab;
- estrogen receptor antagonists or selective estrogen receptor modulators for example tamoxifen, toremifene, droloxifene, faslodex or raloxifene;
- aromatase inhibitors such as exemestane, anastrozole, letrozole and vorozole;
- differentiating agents such as retinoids, vitamin D and retinoic acid metabolism blocking agents (RAMBA) for example accutane;
- DNA methyl transferase inhibitors for example azacytidine;
- kinase inhibitors for example flavoperidol, imatinib mesylate or gefitinib;
- farnesyltransferase inhibitors; or
- other HDAC inhibitors.

The term "platinum coordination compound" is used herein to denote any tumor cell growth inhibiting platinum coordination compound which provides platinum in the form of an ion.

5 The term "taxane compounds" indicates a class of compounds having the taxane ring system and related to or derived from extracts from certain species of yew (*Taxus*) trees.

10 The term "topoisomerase inhibitors" is used to indicate enzymes that are capable of altering DNA topology in eukaryotic cells. They are critical for important cellular functions and cell proliferation. There are two classes of topoisomerases in eukaryotic cells, namely type I and type II. Topoisomerase I is a monomeric enzyme of approximately 100,000 molecular weight. The enzyme binds to DNA and introduces a transient single-strand break, unwinds the double helix (or allows it to unwind) and subsequently reseals the break before dissociating from the DNA strand. Topoisomerase II has a similar mechanism of action which involves the induction of DNA strand breaks or the formation of free radicals.

20 The term "camptothecin compounds" is used to indicate compounds that are related to or derived from the parent camptothecin compound which is a water-insoluble alkaloid derived from the Chinese tree Camptothecin acuminata and the Indian tree *Nothapodytes foetida*.

25 The term "podophyllotoxin compounds" is used to indicate compounds that are related to or derived from the parent podophyllotoxin, which is extracted from the mandrake plant.

The term "anti-tumor vinca alkaloids" is used to indicate compounds that are related to or derived from extracts of the periwinkle plant (*Vinca rosea*).

30 The term "alkylating agents" encompass a diverse group of chemicals that have the common feature that they have the capacity to contribute, under physiological conditions, alkyl groups to biologically vital macromolecules such as DNA. With most of the more important agents such as the nitrogen mustards and the nitrosoureas, the active alkylating moieties are generated *in vivo* after complex degradative reactions, some of which are enzymatic. The most important pharmacological actions of the alkylating agents are those that disturb the fundamental mechanisms concerned with cell proliferation in particular DNA synthesis and cell division. The capacity of alkylating agents to interfere with DNA function and integrity in rapidly proliferating

tissues provides the basis for their therapeutic applications and for many of their toxic properties.

The term "anti-tumour anthracycline derivatives" comprise antibiotics obtained from
5 the fungus *Strep. peuticus var. caesius* and their derivatives, characterised by having a tetracycline ring structure with an unusual sugar, daunosamine, attached by a glycosidic linkage.

10 Amplification of the human epidermal growth factor receptor 2 protein (HER 2) in primary breast carcinomas has been shown to correlate with a poor clinical prognosis for certain patients. Trastuzumab is a highly purified recombinant DNA-derived humanized monoclonal IgG1 kappa antibody that binds with high affinity and specificity to the extracellular domain of the HER2 receptor.

15 Many breast cancers have estrogen receptors and growth of these tumors can be stimulated by estrogen. The terms "estrogen receptor antagonists" and "selective estrogen receptor modulators" are used to indicate competitive inhibitors of estradiol binding to the estrogen receptor (ER). Selective estrogen receptor modulators, when bound to the ER, induces a change in the three-dimensional shape of the receptor,
20 inhibiting its binding to the estrogen responsive element (ERE) on DNA.

In postmenopausal women, the principal source of circulating estrogen is from conversion of adrenal and ovarian androgens (androstenedione and testosterone) to estrogens (estrone and estradiol) by the aromatase enzyme in peripheral tissues.

25 Estrogen deprivation through aromatase inhibition or inactivation is an effective and selective treatment for some postmenopausal patients with hormone-dependent breast cancer.

30 The term "antiestrogen agent" is used herein to include not only estrogen receptor antagonists and selective estrogen receptor modulators but also aromatase inhibitors as discussed above.

35 The term "differentiating agents" encompass compounds that can, in various ways, inhibit cell proliferation and induce differentiation. Vitamin D and retinoids are known to play a major role in regulating growth and differentiation of a wide variety of normal and malignant cell types. Retinoic acid metabolism blocking agents (RAMBA's) increase the levels of endogenous retinoic acids by inhibiting the cytochrome P450-mediated catabolism of retinoic acids.

DNA methylation changes are among the most common abnormalities in human neoplasia. Hypermethylation within the promoters of selected genes is usually associated with inactivation of the involved genes. The term "DNA methyl transferase inhibitors" is used to indicate compounds that act through pharmacological inhibition of DNA methyl transferase and reactivation of tumour suppressor gene expression.

The term "kinase inhibitors" comprises potent inhibitors of kinases that are involved in cell cycle progression and programmed cell death (apoptosis)

The term "farnesyltransferase inhibitors" is used to indicate compounds that were designed to prevent farnesylation of Ras and other intracellular proteins. They have been shown to have effect on malignant cell proliferation and survival.

The term "other HDAC inhibitors" comprises but is not limited to:

- short-chain fatty acids for example butyrate, 4-phenylbutyrate or valproic acid;
- hydroxamic acids for example suberoylanilide hydroxamic acid (SAHA), biaryl hydroxamate A-161906, bicyclic aryl-N-hydroxycarboxamides, pyroxamide, CG-1521, PXD-101, sulfonamide hydroxamic acid, LAQ-824, trichostatin A (TSA), oxamflatin, scriptaid, m-carboxy cinnamic acid bishydroxamic acid, or trapoxin-hydroxamic acid analogue;
- cyclic tetrapeptides for example trapoxin, apidicin or depsipeptide;
- benzamides for example MS-275 or CI-994, or
- depudecin.

For the treatment of cancer the compounds according to the present invention may be administered to a patient as described above, in conjunction with irradiation. Irradiation means ionising radiation and in particular gamma radiation, especially that emitted by linear accelerators or by radionuclides that are in common use today. The irradiation of the tumour by radionuclides can be external or internal.

The present invention also relates to a combination according to the invention of an anti-cancer agent and a HDAC inhibitor according to the invention.

The present invention also relates to a combination according to the invention for use in medical therapy for example for inhibiting the growth of tumour cells.

The present invention also relates to a combinations according to the invention for inhibiting the growth of tumour cells.

5 The present invention also relates to a method of inhibiting the growth of tumour cells in a human subject which comprises administering to the subject an effective amount of a combination according to the invention.

10 This invention further provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a combination according to the invention.

15 The other medicinal agent and HDAC inhibitor may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular other medicinal agent and HDAC inhibitor being administered, their route of administration, the particular tumour being treated and the 20 particular host being treated. The optimum method and order of administration and the dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

25 The platinum coordination compound is advantageously administered in a dosage of 1 to 500mg per square meter (mg/m^2) of body surface area, for example 50 to 400 mg/m^2 , particularly for cisplatin in a dosage of about 75 mg/m^2 and for carboplatin in about 300 mg/m^2 per course of treatment.

30 The taxane compound is advantageously administered in a dosage of 50 to 400 mg per square meter (mg/m^2) of body surface area, for example 75 to 250 mg/m^2 , particularly for paclitaxel in a dosage of about 175 to 250 mg/m^2 and for docetaxel in about 75 to 150 mg/m^2 per course of treatment.

35 The camptothecin compound is advantageously administered in a dosage of 0.1 to 400 mg per square meter (mg/m^2) of body surface area, for example 1 to 300 mg/m^2 , particularly for irinotecan in a dosage of about 100 to 350 mg/m^2 and for topotecan in about 1 to 2 mg/m^2 per course of treatment.

The anti-tumor podophyllotoxin derivative is advantageously administered in a dosage of 30 to 300 mg per square meter (mg/m^2) of body surface area, for example 50 to 250 mg/m^2 , particularly for etoposide in a dosage of about 35 to 100 mg/m^2 and for teniposide in about 50 to 250 mg/m^2 per course of treatment.

5

The anti-tumor vinca alkaloid is advantageously administered in a dosage of 2 to 30 mg per square meter (mg/m^2) of body surface area, particularly for vinblastine in a dosage of about 3 to 12 mg/m^2 , for vincristine in a dosage of about 1 to 2 mg/m^2 , and for vinorelbine in dosage of about 10 to 30 mg/m^2 per course of treatment.

10

The anti-tumor nucleoside derivative is advantageously administered in a dosage of 200 to 2500 mg per square meter (mg/m^2) of body surface area, for example 700 to 1500 mg/m^2 , particularly for 5-FU in a dosage of 200 to 500 mg/m^2 , for gemcitabine in a dosage of about 800 to 1200 mg/m^2 and for capecitabine in about 1000 to 2500 mg/m^2 per course of treatment.

15

The alkylating agents such as nitrogen mustard or nitrosourea is advantageously administered in a dosage of 100 to 500 mg per square meter (mg/m^2) of body surface area, for example 120 to 200 mg/m^2 , particularly for cyclophosphamide in a dosage of about 100 to 500 mg/m^2 , for chlorambucil in a dosage of about 0.1 to 0.2 mg/kg, for carmustine in a dosage of about 150 to 200 mg/m^2 , and for lomustine in a dosage of about 100 to 150 mg/m^2 per course of treatment.

20

The anti-tumor anthracycline derivative is advantageously administered in a dosage of 10 to 75 mg per square meter (mg/m^2) of body surface area, for example 15 to 60 mg/m^2 , particularly for doxorubicin in a dosage of about 40 to 75 mg/m^2 , for daunorubicin in a dosage of about 25 to 45 mg/m^2 , and for idarubicin in a dosage of about 10 to 15 mg/m^2 per course of treatment.

30

Trastuzumab is advantageously administered in a dosage of 1 to 5mg per square meter (mg/m^2) of body surface area, particularly 2 to 4 mg/m^2 per course of treatment.

35

The antiestrogen agent is advantageously administered in a dosage of about 1 to 100mg daily depending on the particular agent and the condition being treated. Tamoxifen is advantageously administered orally in a dosage of 5 to 50 mg, preferably 10 to 20 mg twice a day, continuing the therapy for sufficient time to achieve and maintain a therapeutic effect. Toremifene is advantageously administered orally in a dosage of about 60mg once a day, continuing the therapy for sufficient time to achieve and

maintain a therapeutic effect. Anastrozole is advantageously administered orally in a dosage of about 1mg once a day. Droloxifene is advantageously administered orally in a dosage of about 20-100mg once a day. Raloxifene is advantageously administered orally in a dosage of about 60mg once a day. Exemestane is advantageously administered orally in a dosage of about 25mg once a day.

5 These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7,14, 21 or 28 days.

10 In view of their useful pharmacological properties, the components of the combinations according to the invention, i.e. the other medicinal agent and the HDAC inhibitor may be formulated into various pharmaceutical forms for administration purposes. The components may be formulated separately in individual pharmaceutical compositions or in a unitary pharmaceutical composition containing both components.

15 The present invention therefore also relates to a pharmaceutical composition comprising the other medicinal agent and the HDAC inhibitor together with one or more pharmaceutical carriers.

20 The present invention also relates to a combination according to the invention in the form of a pharmaceutical composition comprising an anti-cancer agent and a HDAC inhibitor according to the invention together with one or more pharmaceutical carriers.

25 The present invention further relates to the use of a combination according to the invention in the manufacture of a pharmaceutical composition for inhibiting the growth of tumour cells.

The present invention further relates to a product containing as first active ingredient a HDAC inhibitor according to the invention and as second active ingredient an anticancer agent, as a combined preparation for simultaneous, separate or sequential use in the treatment of patients suffering from cancer.

Experimental part

35 The following examples are provided for purposes of illustration.

Hereinafter "DCM" means dichloromethane, "DIC" means diisopropylcarbodiimide, "DIEA" means diisopropylethylamine, "DIPE" means diisopropylether, "DMF" means

dimethylformamide, "EDC" means *N*-(ethylcarbonimidoyl)-*N,N*-dimethyl-1,3-propanediamine, monohydrochloride, "EtOH" means ethanol, "Fmoc" means fluorenylmethoxycarbonyl, "HOBT" means 1-hydroxy-1*H*-benzotriazole, "MeOH" means methanol, "PyBop" means benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate, "PyBrOP" means bromo-tris-pyrrolidino-phosphonium hexafluorophosphate, "TFA" means trifluoroacetic acid and "THF" means tetrahydrofuran. Extrelut™ is a product of Merck KgaA, Darmstadt, Germany, and is a short column comprising diatomaceous earth.

5

10 A. Preparation of the intermediates

Example A1

a) A solution of 1-isocyanato-4-methyl-benzene (0.051 mol) in DCM p.a. (75ml) was added dropwise to a solution of 4-(1-piperazinyl)- benzoic acid, ethyl ester (0.043 mol) and triethylamine (0.051 mol) in DCM p.a. (75ml) while stirring at 0°C (ice) for 20 minutes. The reaction mixture was stirred at room temperature for 1 hour and was then extracted with water. The organic layer was extracted with a saturated NaCl-solution and again with water, then separated, dried (MgSO_4), filtered off and the filtrate was evaporated. The residue was stirred in DIPE and the formed precipitate was filtered off, washed with DIPE and dried. A part (0.5g) of the residue (14.3g, 90%) was crystallized from 2-propanol (10ml) and the formed precipitate was filtered off and dried, yielding 0.42g of 4-[4-[(4-methylphenyl)amino]carbonyl]-1-piperazinyl- benzoic acid, ethyl ester (interm. 1).

b) A mixture of interm. 1 (0.021 mol) and HCl 36% (150ml) was stirred and refluxed for 3 hours, then poured out into water (400ml) and stirred for 30 minutes. The precipitate was filtered off, washed with water and dried, yielding 6.57g (92%) of 4-[4-[(4-methylphenyl)amino]carbonyl]-1-piperazinyl- benzoic acid .HCl (1:1)(interm.2).

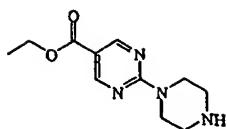
c) A mixture of interm. 2 (0.0009 mol), DIC (0.002 mol) and 4-methylmorpholine (0.44 mol) in DCM (50ml) was stirred. O-(phenylmethyl)- hydroxylamine hydrochloride (0.002 mol) was added. The mixture was stirred at room temperature for 24 hours. Water (50ml) was added. The mixture was filtered. The layers were separated. The organic layer was dried, filtered and the solvent was evaporated. The residue was triturated under 2-propanol. The precipitate was filtered off and dried, yielding 0.133g (33%) of *N*-(4-methylphenyl)-4-[4-[(phenylmethoxy)amino]carbonyl]phenyl- 1-piperazinecarboxamide (interm. 3).

35

Example A2

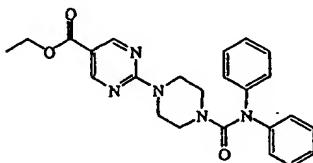
a) Preparation of

-29-



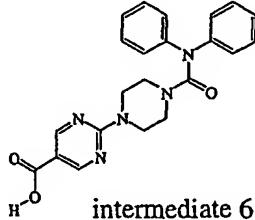
intermediate 4

A mixture of piperazine (0.5 mol) in acetonitrile (500 ml) and potassium carbonate (50g) was stirred at room temperature, then a solution of 2-(methylsulfonyl)- 5-pyrimidinecarboxylic acid, ethyl ester (0.10 mol) in acetonitrile (200 ml) was added dropwise at room temperature. The reaction mixture was stirred at room temperature for 1 hour and was diluted with water. The organic solvent (to remove CH₃CN) was evaporated and the aqueous concentrate was extracted 3 times with DCM. The organic layers were combined, washed with water and dried (MgSO₄). The solvent was evaporated and the residue was crystallised from DIPE, the resulting precipitate was filtered off and dried, yielding 3.8g of intermediate 4. The filtrate was evaporated and the residue was purified by column chromatography over silica gel (eluent: DCM/MeOH 95/5). The product fractions were collected and the solvent was evaporated, yielding 11.9g of intermediate 4. Overall yielding 15.7g of intermediate 4.

b) Preparation of

intermediate 5

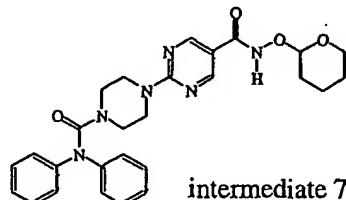
15 A mixture of intermediate 4 (0.0002 mol), diphenyl- carbamic chloride (0.0003 mol) and morpholinomethyl-PS-scavenger (Supplier Novabiochem cat No 01-64-0171: Morpholinomethyl polystyrene HL (200-400 mesh), 2% divinylbenzene) (0.150g) in DCM (5ml) was stirred at room temperature for 20 hours, then tris-(2-aminoethyl)amine-PS-scavenger (Supplier Novabiochem cat No 01-64-0170: Tris-(2-aminomethyl)-amine polystyrene HL(200-400 mesh), 1% divinylbenzene) (0.150g) was added and the reaction mixture was stirred for another 4 hours. The scavengers were filtered off, washed with DCM and the solvent was evaporated, yielding intermediate 5.

c) Preparation of

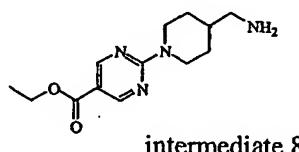
intermediate 6

-30-

A mixture of intermediate 5 (0.0003 mol) in sodium hydroxide 1N (1.5ml), THF (4ml) and MeOH (1ml) was stirred at room temperature for 3 days, then the reaction mixture was neutralised with HCl (1.5ml, 1N). The mixture was filtered through ExtrelutTM NT (supplier: Merck) and dried under N₂-flow, yielding intermediate 6.

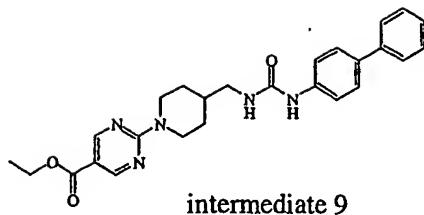
5 d) Preparation of

A mixture of intermediate 6 (0.0003 mol), HOBT-6-carboxamidomethyl-PS-scavenger (0.200g Novabiochem Cat. No. 01-64-0425) and *N,N*-dimethyl-4-pyridinamine (0.00015 mol) in DCM/DMF (5ml) was stirred at room temperature for 15 min., then
 10 *N,N'*-methanetetracyl bis-2-propanamine (0.070ml) was added and the reaction mixture was shaken for 4 hours. The resin was washed 3 times with DCM, 3 times with DMF and again 3 times with DCM and 3 times with DMF, finally 6 times with DCM. A solution of O-(tetrahydro-2*H*-pyran-2-yl)- hydroxylamine (0.00026 mol) in DCM (5ml) was added and the reaction mixture was shaken for 20 hours, then PS-linked
 15 methylisocyanate (0.150g) was added and the mixture was shaken for 4 hours. The scavengers were filtered off, washed 2 times with DCM and the filtrate was evaporated, yielding intermediate 7.

Example A320 a) Preparation of

A solution of 2-(methylsulfonyl)- 5-pyrimidinecarboxylic acid, ethyl ester (0.0434 mol) in acetonitrile (100ml) was added dropwise at 10°C to a solution of 4-piperidinemethanamine (0.0868 mol) and potassium carbonate (0.0434 mol) in
 25 acetonitile (200ml) under N₂ flow. The mixture was stirred at room temperature for 2 hours, poured out into ice water and extracted with DCM. The organic layer was separated, dried (MgSO₄), filtered, and the solvent was evaporated. The residue (14.18g) was purified by column chromatography over silica gel (20-45μm) (eluent: DCM/MeOH/NH₄OH 90/10/1 to 80/20/2). The pure fractions were collected and the
 30 solvent was evaporated, yielding 3.7g (32%) of intermediate 8.

b) Preparation of

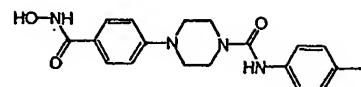


A mixture of intermediate 8 (0.0049 mol) and 4-isocyanato- 1,1'-bipheny (0.0074 mol) in THF (30ml) was stirred at 60°C for 20 hours, then cooled to room temperature, poured out into ice water. The precipitate was filtered, washed with water, then with 5 diethyl ether and dried, yielding 2.215g (98%) of intermediate 9.

B. Preparation of the final compounds

Example B1

10 Preparation of



Compound 1

Interm. 3 (0.0013 mol) in DMF (10ml) was hydrogenated with Pd/C 10% (0.2g) as a catalyst. After uptake of H₂ (1 equiv), the catalyst was filtered off over dicalite and the solvent was evaporated. The residue was dissolved in DCM/MeOH (300ml;50/50) and 15 filtered over a paper filter. The filtrate's solvent was evaporated. The residue was triturated under DCM. The precipitate was filtered off and dried, yielding 0.35g (76%) of compound 1.

Example B2

20 N-Fmoc-hydroxylamine 2-chlorotrityl resin (Novabiochem, 01-64-0165) was deprotected by 50% piperidine in DMF (RT, 24 hr)¹. The resin was washed² several times with DCM and DMF and swelled in DMF. Two equivalents of acid³, PyBrOP⁴ and 4 equivalents of DIEA were added as one portion. The mixture was shaken for 24 hr, liquid was drained and the resin was washed several times by DCM and DMF. The 25 resin was swelled in DMF containing 2 equivalents of amine, was shaken 24 hr at RT, the liquid was drained and the resin was washed by DCM and DMF. Three equivalents of acid, DIC and DIEA were shaken with resin overnight at RT. The resin was drained and washed by DCM and DMF. The final product was cleaved by 5% TFA in DCM, analyzed by HPLC and MS and evaporated in the pre-weighted test-tubes.

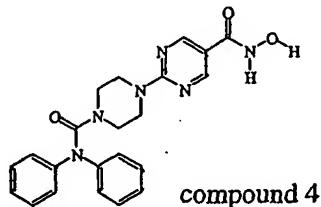
30 ¹. In one example compound 2 Glycinol 2-chlorotrityl-resin (Novabiochem, 01-64-0087) was used. In one other example compound 3 Carboxymethanethiol 4-methoxytrityl resin (Novabiochem, 01-64-0238) was used.

². In two cases also MeOH was used in the different washing procedures compounds 2 and 3 .

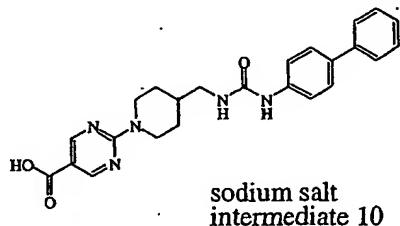
³. Based on the loading of the resin.

⁴. In two cases PyBrOP was replaced by PyBOP compounds 2 and 3 .

5

Example B3Preparation of

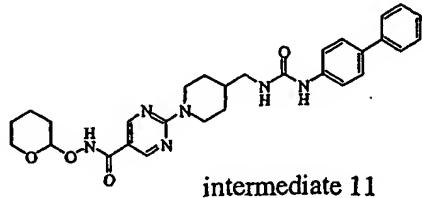
A mixture of intermediate 7 (0.0003 mol) in TFA (5ml, 5% in MeOH) was stirred at
10 room temperature for 20 hours, then the reaction mixture was blown dry, yielding
compound 4.

Example B4a) Preparation of

15

A mixture of intermediate 9 (0.0032 mol) and sodium hydroxide (0.0128 mol) in EtOH (20ml) was stirred at 80°C for 24 hours, then cooled to room temperature. The precipitate was filtered, washed with diethyl ether and dried, yielding 1.31g (90%) of intermediate 10 .Na.

20

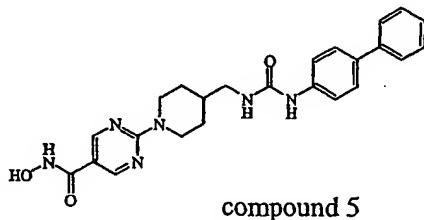
b) Preparation of

25

EDC (0.0037 mol) and HOBT (0.0037 mol) were added at room temperature to a solution of intermediate 10 .Na (0.0029 mol) in DMF (25ml) under N₂ flow. The mixture was stirred for 45 minutes. O-(tetrahydro-2H-pyran-2-yl)- hydroxylamine (0.0037 mol) was added. The mixture was stirred at room temperature for 3 days and poured out into ice water. The organic layer was separated, dried (MgSO₄), filtered, and

the solvent was evaporated. The precipitate was filtered, washed with water and dried. The residue (0.8g) was crystallized from DMF(8ml)/water(2ml). The precipitate was filtered, washed with diethyl ether and dried, yielding 0.734g (48%) of intermediate 11, melting point 188°C.

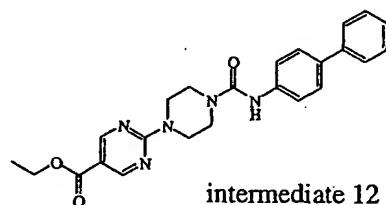
5 c) Preparation of



A mixture of intermediate 11 (0.0014 mol), in TFA (2ml), MeOH (20ml) and DCM (2ml) was stirred at room temperature for 3 days. The precipitate was filtered off and dried. The residue (0.553g) was taken up in DCM/MeOH. The mixture was stirred for 4 hours, then kept at room temperature for 2 days. The precipitate was filtered off and dried, yielding 0.055g of compound 5, melting point >260°C.

Example B5

Preparation of



15 A mixture of intermediate 4 (0.0031 mol) and 4-isocyanato- 1,1'-biphenyl (0.0046 mol) in THF (20ml) was stirred at 60°C for 20 hours, then cooled to room temperature and poured out into ice water. The precipitate was filtered, washed with water/diethyl ether and dried, yielding 1.31g (98%) of intermediate 12.

20 Intermediate 12 was handled analogously as described in example [B4] to give 0.069g (75%) of compound 6, melting point >260°C.

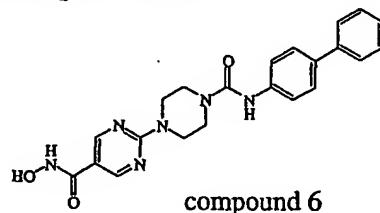
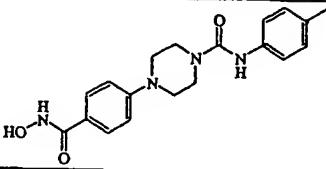
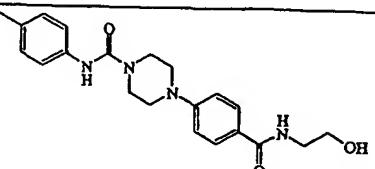
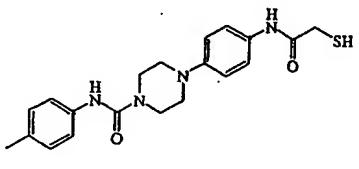
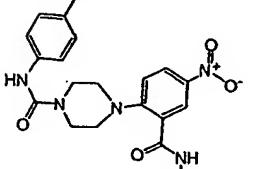
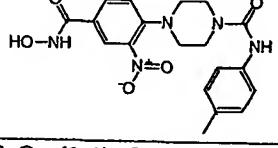
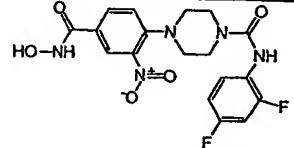
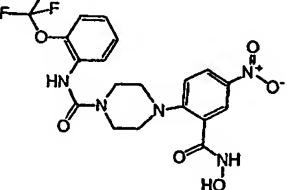
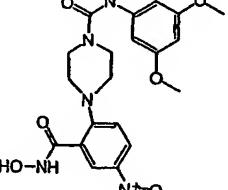
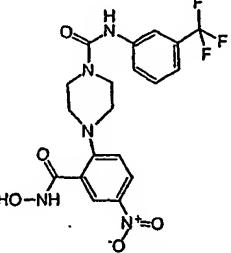
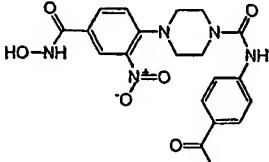
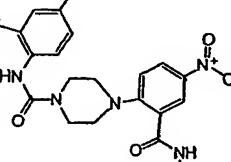
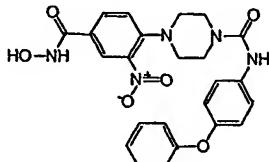
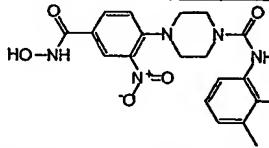
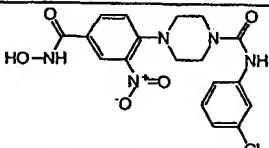
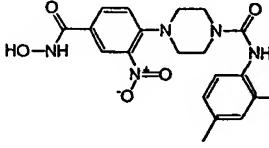
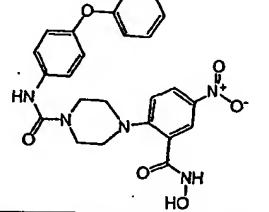
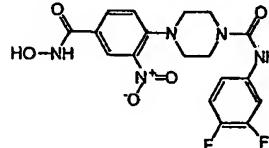
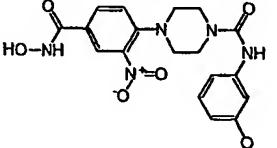


Table F-1 lists the compounds that were prepared according to one of the above Examples. The following abbreviations were used in the tables Co.No. stands for Compound Number, Ex. [Bn°] referred to the same method as described in the Bn° examples, C₂HF₃O₂ stands for the trifluoroacetate salt. Some compounds have been characterized via melting point (mp.), other compounds were characterized via Mass Spectral data [MH⁺] (ms.).

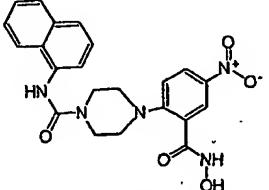
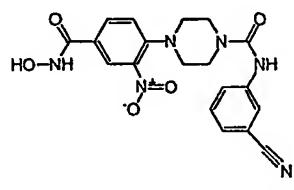
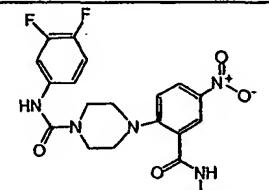
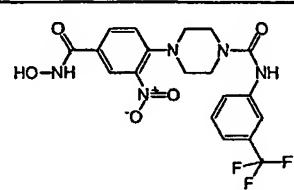
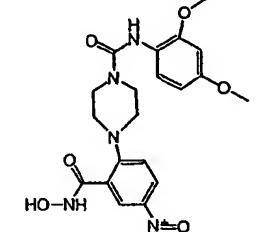
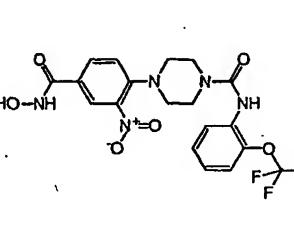
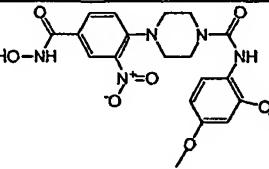
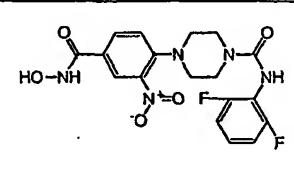
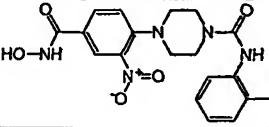
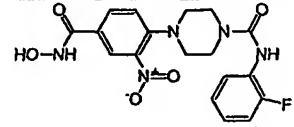
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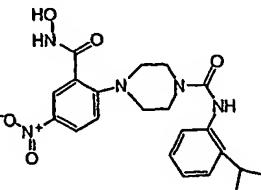
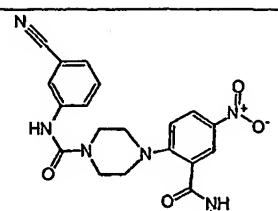
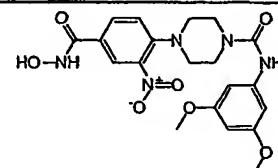
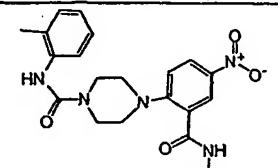
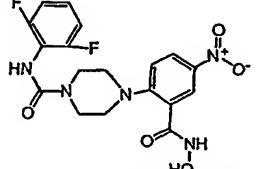
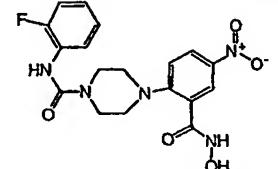
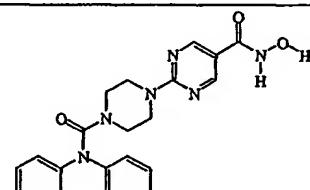
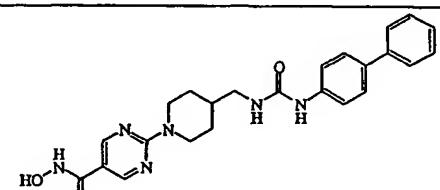
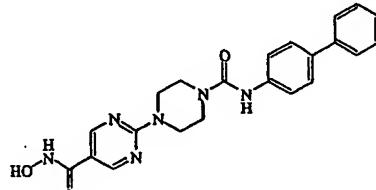
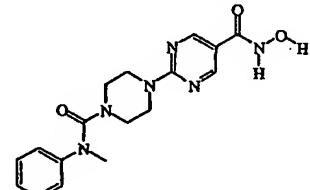
Table F-1

	
Co. No. 1; Ex. [B1]; mp. °C	Co. No. 2; Ex. [B2]
	
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.C ₂ HF ₃ O ₂ (1:1), Co. No. 8; Ex. [B2]; ms. 400	.C ₂ HF ₃ O ₂ (1:1), Co. No. 9; Ex. [B2]; ms. 422
	
.C ₂ HF ₃ O ₂ (1:1), Co. No. 10; Ex. [B2]; ms. 470	.C ₂ HF ₃ O ₂ (1:1), Co. No. 11; Ex. [B2]; ms. 446

	
.C ₂ HF ₃ O ₂ (1:1), Co. No. 12; Ex. [B2]; ms. 454	.C ₂ HF ₃ O ₂ (1:1), Co. No. 13; Ex. [B2]; ms. 428
	
.C ₂ HF ₃ O ₂ (1:1), Co. No. 14; Ex. [B2]; ms. 422	.C ₂ HF ₃ O ₂ (1:1), Co. No. 15; Ex. [B2]; ms. 478
	
.C ₂ HF ₃ O ₂ (1:1), Co. No. 16; Ex. [B2]; ms. 414	.C ₂ HF ₃ O ₂ (1:1), Co. No. 17; Ex. [B2]; ms. 420
	
.C ₂ HF ₃ O ₂ (1:1), Co. No. 18; Ex. [B2]; ms. 414	.C ₂ HF ₃ O ₂ (1:1), Co. No. 19; Ex. [B2]; ms. 478
	
.C ₂ HF ₃ O ₂ (1:1), Co. No. 20; Ex. [B2]; ms. 422	.C ₂ HF ₃ O ₂ (1:1), Co. No. 21; Ex. [B2]; ms. 416

.C ₂ HF ₃ O ₂ (1:1), Co. No. 22; Ex. [B2]; ms. 436	.C ₂ HF ₃ O ₂ (1:1), Co. No. 23; Ex. [B2]; ms. 420
.C ₂ HF ₃ O ₂ (1:1), Co. No. 24; Ex. [B2]; ms. 428	.C ₂ HF ₃ O ₂ (1:1), Co. No. 25; Ex. [B2]; ms. 428
.C ₂ HF ₃ O ₂ (1:1), Co. No. 26; Ex. [B2]; ms. 414	.C ₂ HF ₃ O ₂ (1:1), Co. No. 27; Ex. [B2]; ms. 422
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.C ₂ HF ₃ O ₂ (1:1), Co. No. 34; Ex. [B2]; ms. 422	.C ₂ HF ₃ O ₂ (1:1), Co. No. 35; Ex. [B2]; ms. 454
	
.C ₂ HF ₃ O ₂ (1:1), Co. No. 36; Ex. [B2]; ms. 446	.C ₂ HF ₃ O ₂ (1:1), Co. No. 37; Ex. [B2]; ms. 470
	
.C ₂ HF ₃ O ₂ (1:1), Co. No. 38; Ex. [B2]; ms. 446	.C ₂ HF ₃ O ₂ (1:1), Co. No. 39; Ex. [B2]; ms. 422
	
.C ₂ HF ₃ O ₂ (1:1), Co. No. 40; Ex. [B2]; ms. 400	.C ₂ HF ₃ O ₂ (1:1), Co. No. 41; Ex. [B2]; ms. 404

	
.C ₂ HF ₃ O ₂ (1:1), Co. No. 42; Ex. [B2]; ms. 428	.C ₂ HF ₃ O ₂ (1:1), Co. No. 43; Ex. [B2]; ms. 411
	
.C ₂ HF ₃ O ₂ (1:1), Co. No. 44; Ex. [B2]; ms. 446	.C ₂ HF ₃ O ₂ (1:1), Co. No. 45; Ex. [B2]; ms. 400
	
.C ₂ HF ₃ O ₂ (1:1), Co. No. 46; Ex. [B2]; ms. 422	.C ₂ HF ₃ O ₂ (1:1), Co. No. 47; Ex. [B2]; ms. 404
	
Co. No. 4; Ex. [B3]; ms 419	Co. No. 5; Ex. [B4]; mp.> 260 °C
	
Co. No. 6; Ex. [B5]; mp. >260 °C	Co. No. 48; Ex. [B3]; ms 357

C. Pharmacological example:

The *in vitro* assay for inhibition of histone deacetylase (see example C.1) measures the inhibition of HDAC enzymatic activity obtained with the compounds of formula (I).

5

Cellular activity of the compounds of formula (I) was determined on A2780 tumour cells using a colorimetric assay for cell toxicity or survival (Mosmann Tim, Journal of Immunological Methods 65: 55-63, 1983)(see example C.2).

10 Kinetic solubility in aqueous media measures the ability of a compound to stay in aqueous solution upon dilution (see example C.3).
DMSO-stock solutions are diluted with a single aqueous buffer solvent in 3 consecutive steps. For every dilution turbidity is measured with a nephelometer.

15 A drug's permeability expresses its ability to move from one medium into or through another. Specifically its ability to move through the intestinal membrane into the blood stream and/or from the blood stream into the target. Permeability (see example C.4) can be measured through the formation of a filter-immobilized artificial membrane phospholipid bilayer. In the filter-immobilized artificial membrane assay, a "sandwich"

20 is formed with a 96-well microtitre plate and a 96-well filter plate, such that each composite well is divided into two chambers with a donor solution at the bottom and an acceptor solution at the top, separated by a 125 µm micro-filter disc (0.45 µm pores), coated with 2%(wt/v) dodecane solution of dioleoylphosphatidyl-choline, under conditions that multi-lamellar bilayers form inside the filter channels when the system

25 contacts an aqueous buffer solution. The permeability of compounds through this artificial membrane is measured in cm/s. The purpose is to look for the permeation of the drugs through a parallel artificial membrane at 2 different pH's: 4.0 and 7.4. Compound detection is done with UV-spectrometry at optimal wavelength between 250 and 500 nm.

30 Metabolism of drugs means that a lipid-soluble xenobiotic or endobiotic compound is enzymatically transformed into (a) polar, water-soluble, and excretable metabolite(s). The major organ for drug metabolism is the liver. The metabolic products are often less active than the parent drug or inactive. However, some metabolites may have enhanced

35 activity or toxic effects. Thus drug metabolism may include both "detoxication" and "toxication" processes. One of the major enzyme systems that determine the organism's capability of dealing with drugs and chemicals is represented by the cytochrome P450 monooxygenases, which are NADPH dependent enzymes. Metabolic

stability of compounds can be determined *in vitro* with the use of subcellular human tissue (see example C.5). Here metabolic stability of the compounds is expressed as % of drug metabolised after 15 minutes incubation of these compounds with microsomes. Quantitation of the compounds was determined by LC-MS analysis.

5

Example C.1: In Vitro Assay for Inhibition of histone deacetylase :

HeLa nuclear extracts (supplier: Biomol) were incubated at 60 µg/ml with 2×10^{-8} M of radiolabeled peptide substrate. As a substrate for measuring HDAC activity a synthetic peptide, i.e. the amino acids 14-21 of histone H4, was used. The substrate is biotinylated at the NH₂-terminal part with a 6-aminohexanoic acid spacer, and is protected at the COOH-terminal part by an amide group and specifically [³H]acetylated at lysine 16. The substrate, biotin-(6-aminohexanoic)Gly-Ala-(³H)-acetyl-Lys-Arg-His-Arg-Lys-Val-NH₂), was added in a buffer containing 25 mM Hepes, 1 M sucrose, 0.1 mg/ml BSA and 0.01% Triton X-100 at pH 7.4. After 30 min the deacetylation reaction was terminated by the addition of HCl and acetic acid. (final concentration 0.035 mM and 3.8 mM respectively). After stopping the reaction, the free ³H-acetate was extracted with ethylacetate. After mixing and centrifugation, the radioactivity in an aliquot of the upper (organic) phase was counted in a β-counter.

For each experiment, controls (containing HeLa nuclear extract and DMSO without compound), a blank incubation (containing DMSO but no HeLa nuclear extract or compound) and samples (containing compound dissolved in DMSO and HeLa nuclear extract) were run in parallel. In first instance, compounds were tested at a concentration of 10^{-5} M. When the compounds showed activity at 10^{-5} M, a concentration-response curve was made wherein the compounds were tested at concentrations between 10^{-5} M and 10^{-12} M. In each test the blank value was subtracted from both the control and the sample values. The control sample represented 100% of substrate deacetylation. For each sample the radioactivity was expressed as a percentage of the mean value of the controls. When appropriate IC₅₀-values (concentration of the drug, needed to reduce the amount of metabolites to 50% of the control) were computed using probit analysis for graded data. Herein the effects of test compounds are expressed as pIC₅₀ (the negative log value of the IC₅₀-value). All tested compounds showed enzymatic activity at a test concentration of 10^{-5} M and 28 compounds had a pIC₅₀ ≥ 5 (see table F-2).

35

Example C.2: Determination of antiproliferative activity on A2780 cells

All compounds tested were dissolved in DMSO and further dilutions were made in culture medium. Final DMSO concentrations never exceeded 0.1 % (v/v) in cell

proliferation assays. Controls contained A2780 cells and DMSO without compound and blanks contained DMSO but no cells. MTT was dissolved at 5 mg/ml in PBS. A glycine buffer comprised of 0.1 M glycine and 0.1 M NaCl buffered to pH 10.5 with NaOH (1 N) was prepared (all reagents were from Merck).

5 The human A2780 ovarian carcinoma cells (a kind gift from Dr. T.C. Hamilton [Fox Chase Cancer Centre, Pennsylvania, USA]) were cultured in RPMI 1640 medium supplemented with 2 mM L-glutamine, 50 µg/ml gentamicin and 10 % fetal calf serum. Cells were routinely kept as monolayer cultures at 37°C in a humidified 5 % CO₂ atmosphere. Cells were passaged once a week using a trypsin/EDTA solution at a split ratio of 1:40. All media and supplements were obtained from Life Technologies. Cells were free of mycoplasma contamination as determined using the Gen-Probe Mycoplasma Tissue Culture kit (supplier: BioMérieux).

10 Cells were seeded in NUNC™ 96-well culture plates (Supplier: Life Technologies) and allowed to adhere to the plastic overnight. Densities used for plating were 1500 cells per well in a total volume of 200 µl medium. After cell adhesion to the plates, medium was changed and drugs and/or solvents were added to a final volume of 200 µl. Following four days of incubation, medium was replaced by 200 µl fresh medium and cell density and viability was assessed using an MTT-based assay. To each well, 25 µl MTT solution was added and the cells were further incubated for 2 hours at 37°C. The

15 medium was then carefully aspirated and the blue MTT-formazan product was solubilized by addition of 25 µl glycine buffer followed by 100 µl of DMSO. The microtest plates were shaken for 10 min on a microplate shaker and the absorbance at 540 nm was measured using an Emax 96-well spectrophotometer (Supplier: Sopachem). Within an experiment, the results for each experimental condition are the mean of 3 replicate wells. For initial screening purposes, compounds were tested at a single fixed concentration of 10⁻⁶ M. For active compounds, the experiments were repeated to establish full concentration-response curves. For each experiment, controls (containing no drug) and a blank incubation (containing no cells or drugs) were run in parallel. The blank value was subtracted from all control and sample values. For each sample, the

20 mean value for cell growth (in absorbance units) was expressed as a percentage of the mean value for cell growth of the control. When appropriate, IC₅₀-values (concentration of the drug, needed to reduce cell growth to 50% of the control) were computed using probit analysis for graded data (Finney, D.J., Probit Analyses, 2nd Ed. Chapter 10, Graded Responses, Cambridge University Press, Cambridge 1962). Herein the effects of test

25 compounds are expressed as pIC₅₀ (the negative log value of the IC₅₀-value). Most of the tested compounds showed cellular activity at a test concentration of 10⁻⁶ M and 5 compounds had a pIC₅₀ ≥ 5 (see table F-2).

Example C.3: Kinetic solubility in aqueous media

In the first dilution step, 10 µl of a concentrated stock-solution of the active compound, solubilized in DMSO (5mM), was added to 100 µl phosphate citrate buffer pH 7.4 and
5 mixed. In the second dilution step, an aliquot (20 µl) of the first dilution step was further dispensed in 100 µl phosphate citrate buffer pH 7.4 and mixed. Finally, in the third dilution step, a sample (20 µl) of the second dilution step was further diluted in 100 µl phosphate citrate buffer pH 7.4 and mixed. All dilutions were performed in 96-well plates. Immediately after the last dilution step the turbidity of the three
10 consecutive dilution steps were measured with a nephelometer. Dilution was done in triplicate for each compound to exclude occasional errors. Based on the turbidity measurements a ranking is performed into 3 classes. Compounds with high solubility obtained a score of 3 and for these compounds the first dilution is clear. Compounds with medium solubility obtained a score of 2. For these compounds the first dilution is
15 unclear and the second dilution is clear. Compounds with low solubility obtained a score of 1 and for these compounds both the first and the second dilution are unclear. The solubility of 3 compounds was measured. One compound showed a score of 1, one compound showed a score of 2 and one compound showed a score of 3 (see table F-2).

20 Example C.4: Parallel artificial membrane permeability analysis

The stock samples (aliquots of 10 µl of a stock solution of 5 mM in 100 % DMSO) were diluted in a deep-well or Pre-mix plate containing 2 ml of an aqueous buffer system pH 4 or pH 7.4 (PSR4 System Solution Concentrate (pION)).

25 Before samples were added to the reference plate, 150 µl of buffer was added to wells and a blank UV-measurement was performed. Thereafter the buffer was discarded and the plate was used as reference plate. All measurements were done in UV-resistant plates (supplier: Costar or Greiner).

After the blank measurement of the reference plate, 150 µl of the diluted samples was
30 added to the reference plate and 200 µl of the diluted samples was added to donorplate 1. An acceptor filter plate 1 (supplier: Millipore, type:MAIP N45) was coated with 4 µl of the artificial membrane-forming solution (1,2-Dioleoyl-sn-Glycer-3-Phosphocholine in Dodecane containing 0.1% 2,6-Di-tert-butyl-4-methylphenol and placed on top of donor plate 1 to form a "sandwich". Buffer (200 µl) was dispensed into the acceptor
35 wells on the top. The sandwich was covered with a lid and stored for 18h at room temperature in the dark.

A blank measurement of acceptor plate 2 was performed through the addition of 150 µl of buffer to the wells, followed by an UV-measurement. After the blank measurement

of acceptor plate 2 the buffer was discarded and 150 µl of acceptor solution was transferred from the acceptor filter plate 1 to the acceptor plate 2. Then the acceptor filter plate 1 was removed form the sandwich. After the blank measurement of donor plate 2 (see above), 150 µl of the donor solution was transferred from donor plate 1 to donor plate 2. The UV spectra of the donor plate 2, acceptor plate 2 and reference plate wells were scanned (with a SpectraMAX 190). All the spectra were processed to calculate permeability with the PSR4p Command Software. All compounds were measured in triplo. Carbamazepine, griseofulvin, acycloguanisine, atenolol, furosemide, and chlorothiazide were used as standards in each experiment. Compounds were ranked in 3 categorés as having a low permeability (mean effect < 0.5×10^{-6} cm/s; score 1), a medium permeability (1×10^{-6} cm/s > mean effect $\geq 0.5 \times 10^{-6}$ cm/s; score 2) or a high permeability ($\geq 0.5 \times 10^{-6}$ cm/s; score 3). One compound was measured and showed only a score of 1 at one of the pH's measured.

15 Example C.5: Metabolic stability

Sub-cellular tissue preparations were made according to Gorrod *et al.* (Xenobiotica 5: 453-462, 1975) by centrifugal separation after mechanical homogenization of tissue. Liver tissue was rinsed in ice-cold 0.1 M Tris-HCl (pH 7.4) buffer to wash excess blood. Tissue was then blotted dry, weighed and chopped coarsely using surgical scissors. The tissue pieces were homogenized in 3 volumes of ice-cold 0.1 M phosphate buffer (pH 7.4) using either a Potter-S (Braun, Italy) equipped with a Teflon pestle or a Sorvall Omni-Mix homogeniser, for 7 x 10 sec. In both cases, the vessel was kept in/on ice during the homogenization process.

20 Tissue homogenates were centrifuged at 9000 x g for 20 minutes at 4 °C using a Sorvall centrifuge or Beckman Ultracentrifuge. The resulting supernatant was stored at -80 °C and is designated 'S9'. The S9 fraction can be further centrifuged at 100.000 x g for 60 minutes (4 °C) using a Beckman ultracentrifuge. The resulting supernatant was carefully aspirated, aliquoted and designated 'cytosol'. The pellet was re-suspended in 0.1 M phosphate buffer (pH 7.4) in a final volume of 1 ml per 0.5 g original tissue weight and designated 'microsomes'.

25 All sub-cellular fractions were aliquoted, immediately frozen in liquid nitrogen and stored at -80 °C until use.

30 For the samples to be tested, the incubation mixture contained PBS (0.1M), compound (5 µM), microsomes (1mg/ml) and a NADPH-generating system (0.8 mM glucose-6-phosphate, 0.8 mM magnesium chloride and 0.8 Units of glucose-6-phosphate dehydrogenase). Control samples contained the same material but the microsomes were

replaced by heat inactivated (10 min at 95 degrees Celsius) microsomes. Recovery of the compounds in the control samples was always 100%.

The mixtures were preincubated for 5 min at 37 degrees Celsius. The reaction was started at timepoint zero ($t = 0$) by addition of 0.8 mM NADP and the samples were
5 incubated for 15 min ($t = 15$). The reaction was terminated by the addition of 2 volumes of DMSO. Then the samples were centrifuged for 10 min at 900 x g and the supernatants were stored at room temperature for no longer as 24 h before analysis. All incubations were performed in duplo. Analysis of the supernatants was performed with LC-MS analysis. Elution of the samples was performed on a Xterra MS C18 (50 x 4.6
10 mm, 5 μ m, Waters, US). An Alliance 2790 (Supplier: Waters, US) HPLC system was used. Elution was with buffer A (25 mM ammoniumacetate (pH 5.2) in
 H_2O /acetonitrile (95/5)), solvent B being acetonitrile and solvent C methanol at a flow rate of 2.4 ml/min. The gradient employed was increasing the organic phase concentration from 0 % over 50 % B and 50 % C in 5 min up to 100 % B in 1 min in a
15 linear fashion and organic phase concentration was kept stationary for an additional 1.5 min. Total injection volume of the samples was 25 μ l.

A Quattro (supplier: Micromass, Manchester, UK) triple quadrupole mass spectrometer fitted with and ESI source was used as detector. The source and the desolvation temperature were set at 120 and 350 °C respectively and nitrogen was used as nebuliser
20 and drying gas. Data were acquired in positive scan mode (single ion reaction). Cone voltage was set at 10 V and the dwell time was 1 sec.

Metabolic stability was expressed as % metabolism of the compound after 15 min of incubation in the presence of active microsomes (E(act)) (% metabolism = 100 % -

(($\frac{\text{Total Ion Current (TIC) of E(act) at } t=15}{\text{TIC of E(act) at } t=0}$) x 100)). Compounds that had a

25 percentage metabolism less than 20 % were defined as highly metabolic stable. Compound that had a metabolism between 20 and 70 % were defined as intermediately stable and compounds that showed a percentage metabolism higher than 70 were defined as low metabolic stable. Three reference compounds were always included whenever a metabolic stability screening was performed. Verapamil was included as a
30 compound with low metabolic stability (% metabolism = 73 %). Cisapride was included as a compound with medium metabolic stability (% metabolism 45 %) and propanol was included as a compound with intermediate to high metabolic stability (25 % metabolism). These reference compounds were used to validate the metabolic stability assay.
35 One compound was tested. This compound had a percentage metabolism less than 20 %.

Table F-2: Table F-2 lists the results of the compounds that were tested according to example C.1, C.2, and C.3.

Co. No.	Enzyme activity pIC50	Cellular activity pIC50	Solubility Score
1	6.754	5.328	1
3	5.332	<5	
2	<5	<5	
8	>5		
9	>5		
12	5.37		
13	5.686		
15	>5		
16	>5		
17	>5		
18	>5		
20	>5		
21	>5		
22	5.614		
25	>5		
26	>5		
27	>5		
30	>5		
33	>5		
35	>5		
37	>5		
38	>5		
39	>5		
40	>5		
41	<5		
44	>5		
4	7.127	6.114	
48	7.163	6.141	
5	7.65	6.148	2
6	7.728	6.558	3

D. Composition example: Film-coated tabletsPreparation of tablet core

A mixture of 100 g of a compound of formula (I), 570 g lactose and 200 g starch is
5 mixed well and thereafter humidified with a solution of 5 g sodium dodecyl sulphate
and 10 g polyvinyl-pyrrolidone in about 200 ml of water. The wet powder mixture is
sieved, dried and sieved again. Then there is added 100 g microcrystalline cellulose and
15 g hydrogenated vegetable oil. The whole is mixed well and compressed into tablets,
giving 10.000 tablets, each comprising 10 mg of a compound of formula (I).

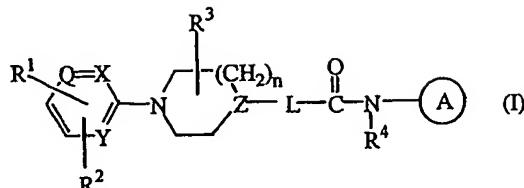
10 Coating

To a solution of 10 g methyl cellulose in 75 ml of denatured ethanol there is added a
solution of 5 g of ethyl cellulose in 150 ml of dichloromethane. Then there are added
75 ml of dichloromethane and 2.5 ml 1,2,3-propanetriol 10 g of polyethylene glycol is
15 molten and dissolved in 75 ml of dichloromethane. The latter solution is added to the
former and then there are added 2.5 g of magnesium octadecanoate, 5 g of polyvinyl-
pyrrolidone and 30 ml of concentrated colour suspension and the whole is
homogenated. The tablet cores are coated with the thus obtained mixture in a coating
apparatus.

Claims

1. A compound of formula (I),

5



the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

10 n is 0, 1, 2 or 3 and when n is 0 then a direct bond is intended;

each Q is nitrogen or $\text{---C}\equiv\text{}$;

each X is nitrogen or $\text{---C}\equiv\text{}$;

15

each Y is nitrogen or $\text{---C}\equiv\text{}$;

each Z is nitrogen or $\text{---CH}\backslash\text{---}$;

20

R¹ is $-\text{C}(\text{O})\text{NR}^7\text{R}^8$, $-\text{N}(\text{H})\text{C}(\text{O})\text{R}^9$, $-\text{C}(\text{O})-\text{C}_{1-6}\text{alkanediylSR}^9$, $-\text{NR}^{10}\text{C}(\text{O})\text{N}(\text{OH})\text{R}^9$, $-\text{NR}^{10}\text{C}(\text{O})\text{C}_{1-6}\text{alkanediylSR}^9$, $-\text{NR}^{10}\text{C}(\text{O})\text{C}=\text{N}(\text{OH})\text{R}^9$ or another Zn-chelating-group

wherein R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl or aminoaryl;

25

R⁹ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, arylC₁₋₆alkyl, C₁₋₆alkylpyrazinyl, pyridinone, pyrrolidinone or methylimidazolyl;

R¹⁰ is independently selected from hydrogen or C₁₋₆alkyl;

30

R² is hydrogen, halo, hydroxy, amino, nitro, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl, di(C₁₋₆alkyl)amino, hydroxyamino or naphtalenylsulfonylpypyrazinyl;

35

R³ is hydrogen, hydroxy, amino, hydroxyC₁₋₆alkyl, C₁₋₆alkyl, C₁₋₆alkyloxy, arylC₁₋₆alkyl, aminocarbonyl, hydroxycarbonyl, aminoC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, hydroxycarbonylC₁₋₆alkyl, hydroxyaminocarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminoC₁₋₆alkyl or di(C₁₋₆alkyl)aminoC₁₋₆alkyl;

when Z is equal to nitrogen, then -L- is a direct bond;

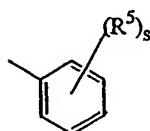
when Z is equal to ---CH--- , then -L- is $-\text{NH}-$ or the bivalent radical
 $-\text{C}_1\text{-}6\text{alkanediylnH}-$;

5

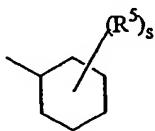
R^4 is hydrogen, $\text{C}_1\text{-}6\text{alkyl}$, $\text{C}_{3\text{-}10}\text{cycloalkyl}$, hydroxy $\text{C}_1\text{-}6\text{alkyl}$, $\text{C}_1\text{-}6\text{alkyloxyC}_1\text{-}6\text{alkyl}$,
 $\text{di(C}_1\text{-}6\text{alkyl)aminoC}_1\text{-}6\text{alkyl}$ or aryl;

—(A) is a radical selected from

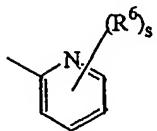
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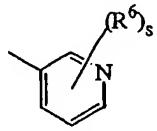
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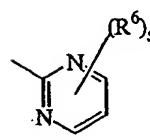
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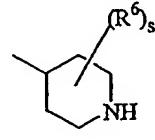
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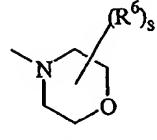
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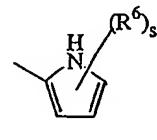
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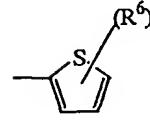
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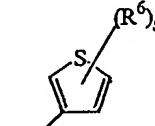
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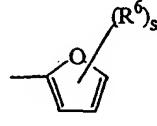
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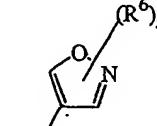
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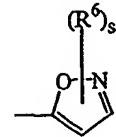


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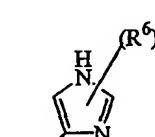


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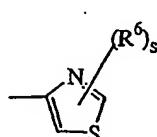
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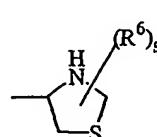
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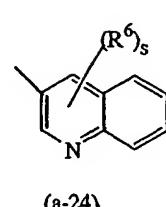
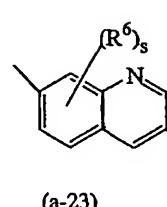
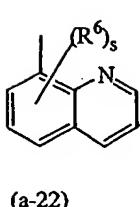
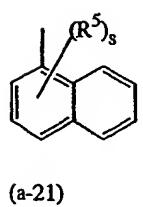
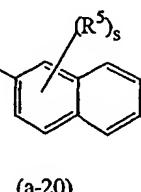
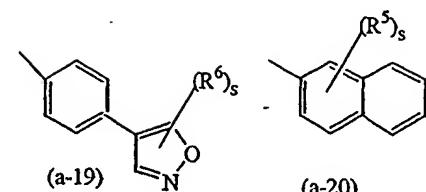
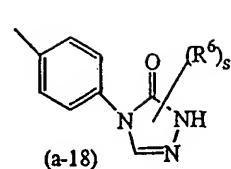
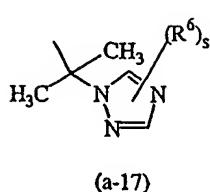


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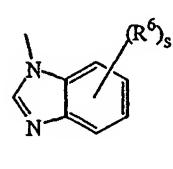
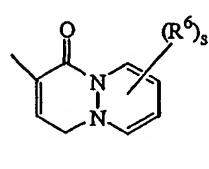
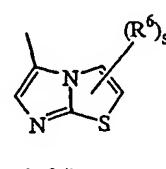
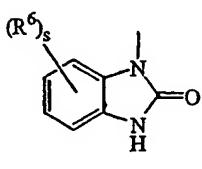
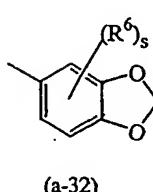
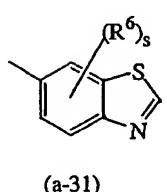
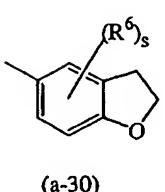
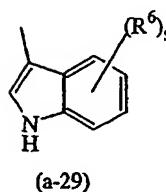
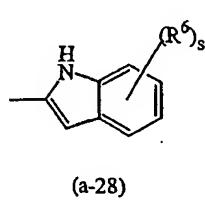
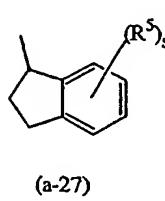
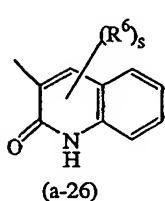


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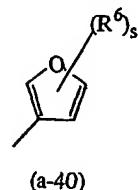
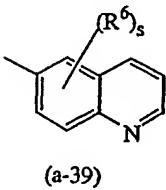
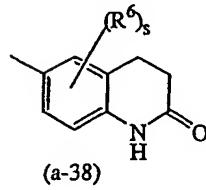
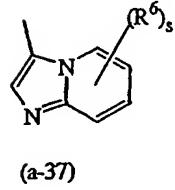
-49-



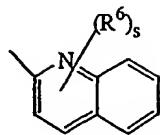
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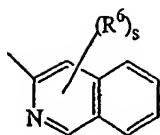
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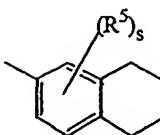
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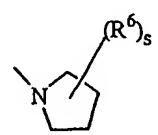
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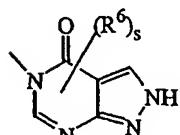
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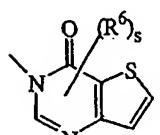
(a-43)



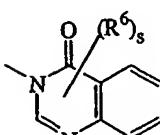
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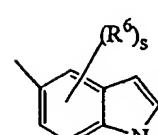
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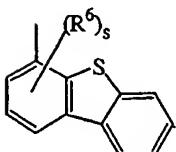
(a-46)



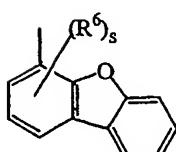
(a-47)



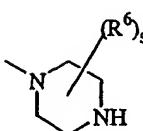
(a-48)



5 (a-49)



(a-50)



(a-51)

wherein each s is independently 0, 1, 2, 3, 4 or 5;

each R⁵ and R⁶ are independently selected from hydrogen; halo; hydroxy; amino; nitro; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyl substituted with aryl and C₃₋₁₀cycloalkyl; C₁₋₆alkyloxy; C₁₋₆alkyloxyC₁₋₆alkyloxy; C₁₋₆alkylcarbonyl;

10 C₁₋₆alkyloxycarbonyl; C₁₋₆alkylsulfonyl; cyanoC₁₋₆alkyl; hydroxyC₁₋₆alkyl; hydroxyC₁₋₆alkyloxy; hydroxyC₁₋₆alkylamino; aminoC₁₋₆alkyloxy;

di(C₁₋₆alkyl)aminocarbonyl; di(hydroxyC₁₋₆alkyl)amino; (aryl)(C₁₋₆alkyl)amino; di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy; di(C₁₋₆alkyl)aminoC₁₋₆alkylamino;

di(C₁₋₆alkyl)aminoC₁₋₆alkylaminoC₁₋₆alkyl; arylsulfonyl; arylsulfonylamino;

15 aryloxy; aryloxyC₁₋₆alkyl; arylC₂₋₆alkenediyl; di(C₁₋₆alkyl)amino;

di(C₁₋₆alkyl)aminoC₁₋₆alkyl; di(C₁₋₆alkyl)amino(C₁₋₆alkyl)amino;

di(C₁₋₆alkyl)amino(C₁₋₆alkyl)aminoC₁₋₆alkyl;

di(C₁₋₆alkyl)aminoC₁₋₆alkyl(C₁₋₆alkyl)amino;

di(C₁₋₆alkyl)aminoC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl;

20 aminosulfonylamino(C₁₋₆alkyl)amino;

aminosulfonylamino(C₁₋₆alkyl)aminoC₁₋₆alkyl;

di(C₁₋₆alkyl)aminosulfonylamino(C₁₋₆alkyl)amino;

di(C₁₋₆alkyl)aminosulfonylamino(C₁₋₆alkyl)aminoC₁₋₆alkyl; cyano; thiophenyl;

thiophenyl substituted with di(C₁₋₆alkyl)aminoC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl,

25 di(C₁₋₆alkyl)aminoC₁₋₆alkyl, C₁₋₆alkylpiperazinylC₁₋₆alkyl,

hydroxyC₁₋₆alkylpiperazinylC₁₋₆alkyl,

hydroxyC₁₋₆alkyloxyC₁₋₆alkylpiperazinylC₁₋₆alkyl,

di(C₁₋₆alkyl)aminosulfonylpiperazinylC₁₋₆alkyl,
C₁₋₆alkyloxypiperidinyl, C₁₋₆alkyloxypiperidinylC₁₋₆alkyl, morpholinylC₁₋₆alkyl,
hydroxyC₁₋₆alkyl(C₁₋₆alkyl)aminoC₁₋₆alkyl, or di(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkyl;
furanyl; furanyl substituted with hydroxyC₁₋₆alkyl; benzofuranyl; imidazolyl;
5 oxazolyl; oxazolyl substituted with aryl and C₁₋₆alkyl; C₁₋₆alkyltriazolyl; tetrazolyl;
pyrrolidinyl; pyrrolyl; piperidinylC₁₋₆alkyloxy; morpholinyl; C₁₋₆alkylmorpholinyl;
morpholinylC₁₋₆alkyloxy;
morpholinylC₁₋₆alkyl; morpholinylC₁₋₆alkylamino;
morpholinylC₁₋₆alkylaminoC₁₋₆alkyl; piperazinyl; C₁₋₆alkylpiperazinyl;
10 C₁₋₆alkylpiperazinylC₁₋₆alkyloxy; piperazinylC₁₋₆alkyl;
naphtalenylsulfonylpiperazinyl; naphtalenylsulfonylpiperidinyl; naphtalenylsulfonyl:
C₁₋₆alkylpiperazinylC₁₋₆alkyl; C₁₋₆alkylpiperazinylC₁₋₆alkylamino;
C₁₋₆alkylpiperazinylC₁₋₆alkylaminoC₁₋₆alkyl; C₁₋₆alkylpiperazinylsulfonyl;
aminosulfonylpiperazinylC₁₋₆alkyloxy; aminosulfonylpiperazinyl;
15 aminosulfonylpiperazinylC₁₋₆alkyl; di(C₁₋₆alkyl)aminosulfonylpiperazinyl;
di(C₁₋₆alkyl)aminosulfonylpiperazinylC₁₋₆alkyl; hydroxyC₁₋₆alkylpiperazinyl;
hydroxyC₁₋₆alkylpiperazinylC₁₋₆alkyl; C₁₋₆alkyloxypiperidinyl;
C₁₋₆alkyloxypiperidinylC₁₋₆alkyl; piperidinylaminoC₁₋₆alkylamino;
piperidinylaminoC₁₋₆alkylaminoC₁₋₆alkyl;
20 (C₁₋₆alkylpiperidinyl)(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkylamino;
(C₁₋₆alkylpiperidinyl)(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkylaminoC₁₋₆alkyl;
hydroxyC₁₋₆alkyloxyC₁₋₆alkylpiperazinyl;
hydroxyC₁₋₆alkyloxyC₁₋₆alkylpiperazinylC₁₋₆alkyl;
(hydroxyC₁₋₆alkyl)(C₁₋₆alkyl)amino; (hydroxyC₁₋₆alkyl)(C₁₋₆alkyl)aminoC₁₋₆alkyl;
25 hydroxyC₁₋₆alkylaminoC₁₋₆alkyl; di(hydroxyC₁₋₆alkyl)aminoC₁₋₆alkyl;
pyrrolidinylC₁₋₆alkyl; pyrrolidinylC₁₋₆alkyloxy; pyrazolyl; thiopyrazolyl; pyrazolyl
substituted with two substituents selected from C₁₋₆alkyl or trihaloC₁₋₆alkyl;
pyridinyl; pyridinyl substituted with C₁₋₆alkyloxy, aryloxy or aryl; pyrimidinyl;
tetrahydropyrimidinylpiperazinyl; tetrahydropyrimidinylpiperazinylC₁₋₆alkyl;
30 quinolinyl; indolyl; phenyl; phenyl substituted with one, two or three substituents
independently selected from halo, amino, nitro, C₁₋₆alkyl, C₁₋₆alkyloxy,
hydroxyC₁₋₄alkyl, trifluoromethyl, trifluoromethoxy, hydroxyC₁₋₄alkyloxy,
C₁₋₄alkylsulfonyl, C₁₋₄alkyloxyC₁₋₄alkyloxy, C₁₋₄alkyloxycarbonyl,
aminoC₁₋₄alkyloxy, di(C₁₋₄alkyl)aminoC₁₋₄alkyloxy, di(C₁₋₄alkyl)amino,
35 di(C₁₋₄alkyl)aminocarbonyl, di(C₁₋₄alkyl)aminoC₁₋₄alkyl,
di(C₁₋₄alkyl)aminoC₁₋₄alkylaminoC₁₋₄alkyl,
di(C₁₋₄alkyl)amino(C₁₋₄alkyl)amino, di(C₁₋₄alkyl)amino(C₁₋₄alkyl)aminoC₁₋₄alkyl,
di(C₁₋₄alkyl)aminoC₁₋₄alkyl(C₁₋₄alkyl)amino,

di(C₁₋₄alkyl)aminoC₁₋₄alkyl(C₁₋₄alkyl)aminoC₁₋₄alkyl,
 aminosulfonylamino(C₁₋₄alkyl)amino,
 aminosulfonylamino(C₁₋₄alkyl)aminoC₁₋₄alkyl,
 di(C₁₋₄alkyl)aminosulfonylamino(C₁₋₄alkyl)amino,

5 di(C₁₋₄alkyl)aminosulfonylamino(C₁₋₄alkyl)aminoC₁₋₆alkyl, cyano,
 piperidinylC₁₋₄alkyloxy, pyrrolidinylC₁₋₄alkyloxy, aminosulfonylpiperazinyl,
 aminosulfonylpiperazinylC₁₋₄alkyl, di(C₁₋₄alkyl)aminosulfonylpiperazinyl,
 di(C₁₋₄alkyl)aminosulfonylpiperazinylC₁₋₄alkyl, hydroxyC₁₋₄alkylpiperazinyl,
 hydroxyC₁₋₄alkylpiperazinylC₁₋₄alkyl, C₁₋₄alkyloxypiperidinyl,

10 C₁₋₄alkyloxypiperidinylC₁₋₄alkyl, hydroxyC₁₋₄alkyloxyC₁₋₄alkylpiperazinyl,
 hydroxyC₁₋₄alkyloxyC₁₋₄alkylpiperazinylC₁₋₄alkyl,
 (hydroxyC₁₋₄alkyl)(C₁₋₄alkyl)amino, (hydroxyC₁₋₄alkyl)(C₁₋₄alkyl)aminoC₁₋₄alkyl,
 di(hydroxyC₁₋₄alkyl)amino, di(hydroxyC₁₋₄alkyl)aminoC₁₋₄alkyl, furanyl, furanyl
 substituted with -CH=CH-CH=CH-, pyrrolidinylC₁₋₄alkyl, pyrrolidinylC₁₋₄alkyloxy,

15 morpholinyl, morpholinylC₁₋₄alkyloxy, morpholinylC₁₋₄alkyl,
 morpholinylC₁₋₄alkylamino, morpholinylC₁₋₄alkylaminoC₁₋₄alkyl, piperazinyl,
 C₁₋₄alkylpiperazinyl, C₁₋₄alkylpiperazinylC₁₋₄alkyloxy, piperazinylC₁₋₄alkyl,
 C₁₋₄alkylpiperazinylC₁₋₄alkyl, C₁₋₄alkylpiperazinylC₁₋₄alkylamino,
 C₁₋₄alkylpiperazinylC₁₋₄alkylaminoC₁₋₆alkyl, tetrahydropyrimidinylpiperazinyl,

20 tetrahydropyrimidinylpiperazinylC₁₋₄alkyl, piperidinylaminoC₁₋₄alkylamino,
 piperidinylaminoC₁₋₄alkylaminoC₁₋₄alkyl,
 (C₁₋₄alkylpiperidinyl)(hydroxyC₁₋₄alkyl)aminoC₁₋₄alkylamino,
 (C₁₋₄alkylpiperidinyl)(hydroxyC₁₋₄alkyl)aminoC₁₋₄alkylaminoC₁₋₄alkyl,
 pyridinylC₁₋₄alkyloxy,

25 hydroxyC₁₋₄alkylamino, hydroxyC₁₋₄alkylaminoC₁₋₄alkyl,
 di(C₁₋₄alkyl)aminoC₁₋₄alkylamino, aminothiadiazolyl,
 aminosulfonylpiperazinylC₁₋₄alkyloxy, or thiophenylC₁₋₄alkylamino;
 each R⁵ and R⁶ can be placed on the nitrogen in replacement of the hydrogen;

30 aryl in the above is phenyl, or phenyl substituted with one or more substituents each
 independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl, cyano or
 hydroxycarbonyl.

2. A compound as claimed in claim 1 wherein

35 each Z is nitrogen;

R¹ is -C(O)NR⁷R⁸, -C(O)-C₁₋₆alkanediylSR⁹, -NR¹⁰C(O)N(OH)R⁹,
 -NR¹⁰C(O)C₁₋₆alkanediylSR⁹, -NR¹⁰C(O)C=N(OH)R⁹ or another Zn-chelating-
 group

wherein R⁷ and R⁸ are each independently selected from hydrogen, hydroxy, hydroxyC₁₋₆alkyl, or aminoC₁₋₆alkyl;

R² is hydrogen, halo, hydroxy, amino, nitro, C₁₋₆alkyl, C₁₋₆alkyloxy, trifluoromethyl or di(C₁₋₆alkyl)amino;

5 R³ is hydrogen, hydroxy, amino, hydroxyC₁₋₆alkyl, C₁₋₆alkyl, C₁₋₆alkyloxy, arylC₁₋₆alkyl, aminocarbonyl, aminoC₁₋₆alkyl, C₁₋₆alkylaminoC₁₋₆alkyl or di(C₁₋₆alkyl)aminoC₁₋₆alkyl;

R⁴ is hydrogen;

10 ——A—is a radical selected from (a-1), (a-3), (a-4), (a-5), (a-6), (a-7), (a-8), (a-9), (a-10), (a-11), (a-12), (a-13), (a-14), (a-15), (a-16), (a-17), (a-18), (a-19), (a-20), (a-21), (a-22), (a-23), (a-24), (a-25), (a-26), (a-28), (a-29), (a-30), (a-31), (a-32), (a-33), (a-34), (a-35), (a-36), (a-37), (a-38), (a-39), (a-40), (a-41), (a-42), (a-44), (a-45), (a-46), (a-47), (a-48) or (a-51);

each s is independently 0, 1, 2, 3 or 4;

15 R⁵ is hydrogen; halo; hydroxy; amino; nitro; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylsulfonyl; hydroxyC₁₋₆alkyl; aryloxy; di(C₁₋₆alkyl)amino; cyano; thiophenyl; furanyl; furanyl substituted with hydroxyC₁₋₆alkyl; benzofuranyl; imidazolyl; oxazolyl; oxazolyl substituted with aryl and C₁₋₆alkyl; 20 C₁₋₆alkyltriazolyl; tetrazolyl; pyrrolidinyl; pyrrolyl; morpholinyl; C₁₋₆alkylmorpholinyl; piperazinyl; C₁₋₆alkylpiperazinyl; hydroxyC₁₋₆alkylpiperazinyl; C₁₋₆alkyloxypiperidinyl; pyrazolyl; pyrazolyl substituted with one or two substituents selected from C₁₋₆alkyl or trihaloC₁₋₆alkyl; pyridinyl; pyridinyl substituted with C₁₋₆alkyloxy, aryloxy or aryl; pyrimidinyl; 25 quinolinyl; indole; phenyl; or phenyl substituted with one or two substituents independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl; and R⁶ is hydrogen; halo; hydroxy; amino; nitro; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; C₁₋₆alkyloxycarbonyl; C₁₋₆alkylsulfonyl; hydroxyC₁₋₆alkyl; aryloxy; di(C₁₋₆alkyl)amino; cyano; pyridinyl; 30 phenyl; or phenyl substituted with one or two substituents independently selected from halo, C₁₋₆alkyl, C₁₋₆alkyloxy or trifluoromethyl.

3. A compound as claimed in claim 1 wherein n is 1; each Q is $\text{---}\overset{\text{---}}{\underset{\text{---}}{\text{C}}} \text{---}$; R¹ is —C(O)NR⁷R⁸, or —NHC(O)C₁₋₆alkanediylSH wherein R⁷ and R⁸ are each independently selected from hydrogen, hydroxy or hydroxyC₁₋₆alkyl; R² is hydrogen or nitro; R³ is hydrogen; when Z is equal to $\text{---}\overset{\text{---}}{\underset{\text{---}}{\text{CH}}} \text{---}$, then —L— is the bivalent radical

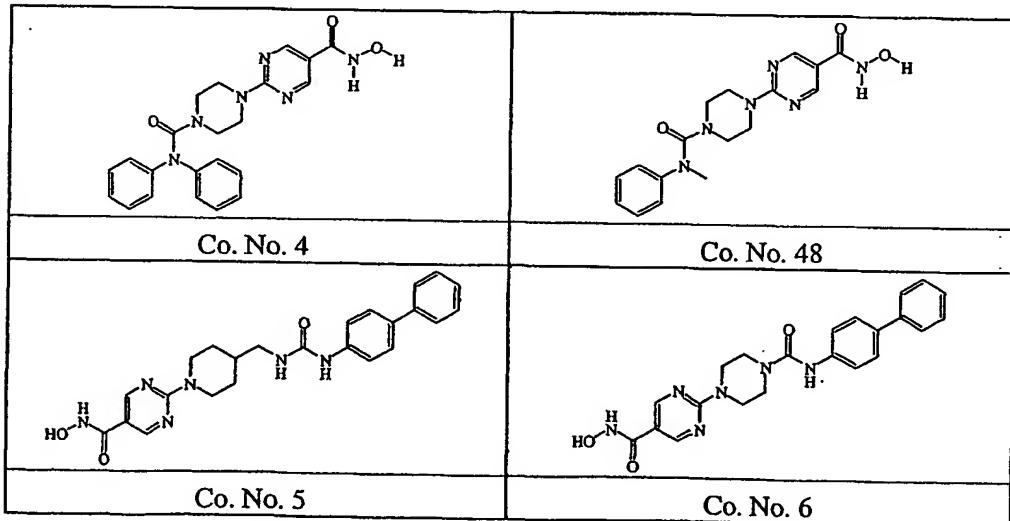
-C₁₋₆alkanediylNH-; R⁴ is hydrogen, C₁₋₆alkyl or aryl; A is a radical selected from (a-1) or (a-21); each s is independently 0, 1 or 2; and each R⁵ is independently selected from hydrogen; halo; trihaloC₁₋₆alkyl; trihaloC₁₋₆alkyloxy; C₁₋₆alkyl; C₁₋₆alkyloxy; C₁₋₆alkylcarbonyl; aryloxy, cyano or phenyl.

5

4. A compound as claimed in claim 1 and 3 wherein n is 1; each Q is $\text{--C}\equiv\text{}$; each X is nitrogen; each Y is nitrogen; R¹ is $-\text{C}(\text{O})\text{NH(OH)}$; R² is hydrogen; R³ is hydrogen; when Z is equal to $-\text{CH}_2-$, then $-\text{L}-$ is the bivalent radical $-\text{C}_1\text{-alkanediylNH-}$; R⁴ is hydrogen, C₁₋₆alkyl or aryl;  is the radical (a-1); each s is independently 0 or 1; and each R⁵ is independently selected from hydrogen or phenyl.

5. A compound according to claim 1, 3 and 4 selected from compounds No. 4, No. 48, No. 5 and No. 6.

15



20

6. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 1 to 5.
7. A process of preparing a pharmaceutical composition as claimed in claim 6 wherein the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 5 are intimately mixed.

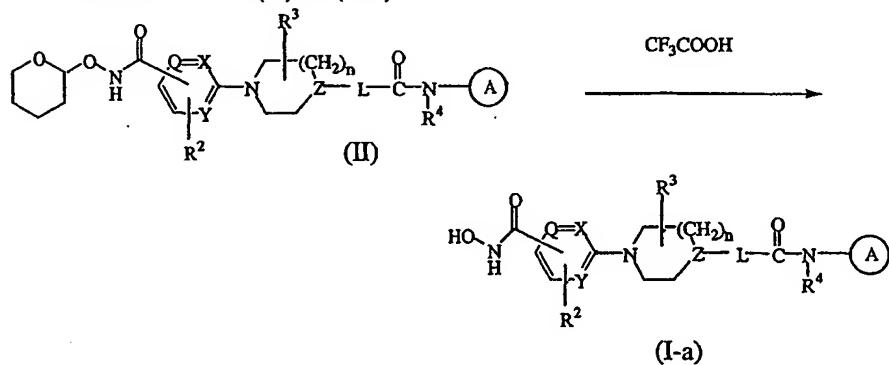
-55-

8. A compound as claimed in any of claims 1 to 5 for use as a medicine.

9. Use of a compound as claimed in any of claims 1 to 5 for the manufacture of a medicament for the treatment of proliferative diseases.

5

10. A process for preparing a compound as claimed in claim 1, characterized by reacting an intermediate of formula (II) with an appropriate acid, such as for example, trifluoro acetic acid, yielding a hydroxamic acid of formula (I-a), wherein R¹ is -C(O)NH(OH).



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11. A method of detecting or identifying a HDAC in a biological sample comprising detecting or measuring the formation of a complex between a labelled compound as defined in claim (I) and a HDAC.

12. A combination of an anti-cancer agents and a HDAC inhibitor as claimed in any of claims 1 to 5.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/02511

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/20 C07D239/42 A61K31/506 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 38322 A (METHYLGENE INC) 31 May 2001 (2001-05-31) the whole document -----	1,9
A	WO 98 55449 A (QUEENSLAND INST MED RES ;FAIRLIE DAVID (AU); PARSONS PETER G (AU);) 10 December 1998 (1998-12-10) the whole document -----	1,9



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the International filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the International filing date but later than the priority date claimed

- *T* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the International search

8 May 2003

Date of mailing of the International search report

22/05/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax (+31-70) 340-3016

Authorized officer

de Nooy, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/02511

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
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